RADIUM, X RAYS AND THE LIVING CELL

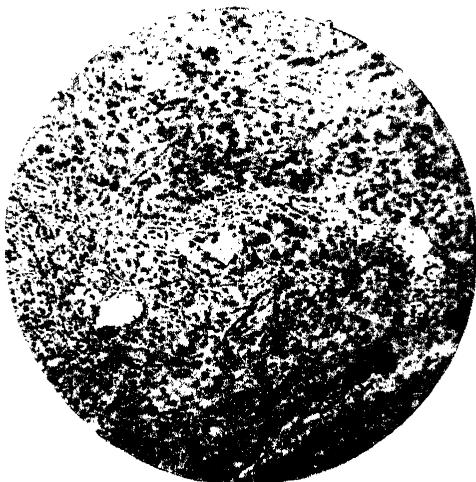


FIG. 56.—PROLIFERATING CARCINOMA OF THE SKIN OF THE CHEEK IN AN OLD MAN. BIOPSY BEFORE TREATMENT. (*Dominici, Hæmatein Eosin Aurantia,* 100 *diameters.*)—Trabeculæ of typical carcinoma cells, without any signs of keratinisation.

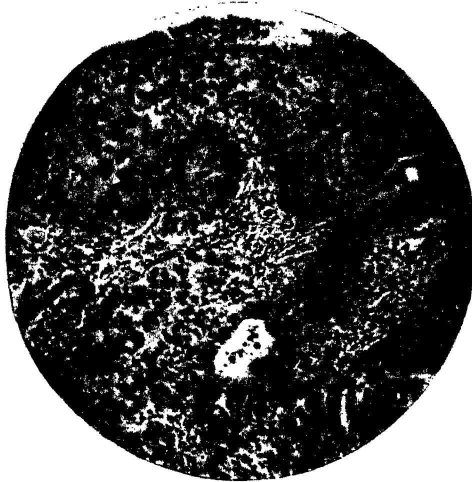


FIG. 57.—SAME CASE AS FIG. 56. SUPERFICIAL BIOPSY, TEN DAYS AFTER THE BEGINNING OF THE X-RAY TREATMENT. (*Same technique, same magnifying power.*)—The carcinoma cells are much enlarged, and the nuclei exhibit various aberrant forms.



FIG. 58—SAME CASE AS FIG. 56. SUPERFICIAL BIOPSY, THREE WEEKS AFTER THE BEGINNING OF THE X-RAY TREATMENT. (*Same technique, same magnifying power.*)—The carcinoma cells are still larger, and have undergone keratinisation while nuclear pycnosis is well marked.



FIG. 59.—SAME CASE AS FIG. 56. BIOPSY OF THE SCAR, AFTER COMPLETE CLINICAL HEALING OF THE TUMOUR. (*Same technique, same magnifying power.*)—The Figure shows a stroma made up of young connective cells. At first sight no carcinoma cells remain, but at the left of the figure, near the centre, three cells with dark nuclei may be seen; these are most likely quiescent tumour cells.

PLATE I.

HISTOLOGICAL APPEARANCES OF IRRADIATED TUMOUR.

Dr. JEAN CLUNET, Journal of the Roentgen Society, No. 39. 1914.

RADIUM, X RAYS

AND

THE LIVING CELL

WITH PHYSICAL INTRODUCTION

BY

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PREFACE

Our object in the present book is to describe some of the main experimental facts which have been established, as to the effects that the X rays and the rays from radium have upon living cells.

In order to make the subject generally intelligible, a description of the properties of these radiations was necessary, and Part I. is designed, not only to provide information in this respect, but to meet the needs of those who approach the subject with a view to experimental investigation.

A large amount of interest centres around the action which the rays have upon malignant cells, and some of the most detailed studies have been made by investigators in this connection. The results which have so far been reached are, we may venture to hope, a good augury for the foundations of a rational basis of radio-therapy.

This, however, is but one aspect of the effect of the rays upon the living cell, and we believe that an increased knowledge of the reactions exhibited by normal healthy cells and tissues is necessary before the real nature of the processes set up by these rays is revealed.

The subject is not approached from the clinical aspect, but data have frequently been selected from the details of clinical observations, when these have borne upon the subject-matter in question

We acknowledge with pleasure the permission given by the Cancer Investigation Committee of the Middlesex Hospital, the

Royal Society, the Royal Society of Medicine and the Roentgen Society, to reproduce illustrations from their publications.

Our special thanks are due to Dr. Jean Clunet for allowing us to reproduce two of the coloured plates which illustrate the results of his researches, and to Dr. H. H. Dale, F.R.S., Mr. C. R. C. Lyster, and Dr. W. Makower, for their kindness in reading the manuscript.

H. A. C.
S. R.

LONDON, 1915.

PREFACE TO THE SECOND EDITION

THE present Edition follows the same general lines as the first. The scope of several of the chapters has been extended to include recent experimental results and one additional chapter is inserted; this chapter contains a brief summary of some of the outstanding features of radiation action upon living structures, and a short discussion upon the theories which have been put forward to account for these effects.

Our thanks are due to those who have pointed out errors and omissions in the first edition of the book, and these we have attempted to rectify.

H. A. C.
S. R.

LONDON, 1924.

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PART I

CHAPTER I

THE RÖNTGEN OR X RAYS

A NEW type of radiation was discovered in 1895 by Röntgen who found that the rays gave rise to then unknown phenomena; he proposed that they should be called X Rays.

The method of production of these rays will be best understood by a preliminary consideration of the phenomena attending the electrical discharge taking place between two terminals in a rarefied gas.

If a glass tube (Fig. 1) be provided with two metallic terminals,

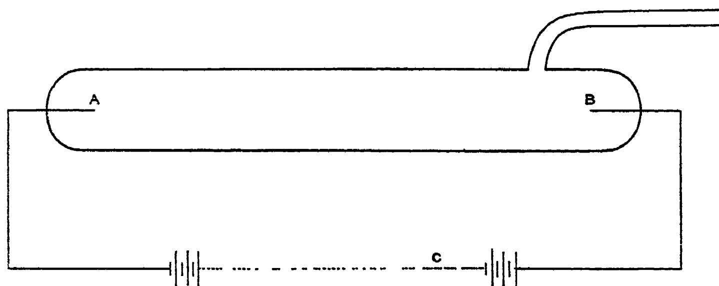


Fig 1.

A and *B*, situated 10–20 centimetres apart and connected to a source of electricity *C* capable of giving a potential difference of about a thousand volts, no discharge will occur so long as the air in the tube is at the ordinary atmospheric pressure. When the air is gradually pumped out of the tube until the pressure within it is reduced to about a centimetre of mercury, certain characteristic phenomena make their appearance. At first a homogeneous luminosity, known as the positive column, is observed to spread

from the positive terminal almost up to the negative terminal, but is separated from it by a dark space known as the Faraday dark space. As exhaustion of the tube proceeds, the positive column loses its homogeneity, and is broken up into striae, which, in fact, are separate segments of luminous gas. These striae gradually diminish in intensity, and in the immediate neighbourhood of the negative pole there appears another dark space, the Crookes space, adjacent to which is an area of luminosity—the "negative glow." As exhaustion proceeds, the bluish negative glow extends throughout the tube, causing the glass walls to fluoresce; this negative glow is known as the "Cathode Stream." If an object be placed in its path, a shadow is cast, as in the case of ordinary light, but it must be understood that the Cathode Stream does not consist of ordinary light, but of minute particles of negative electricity or "electrons."

Many substances exhibit a characteristic fluorescence when placed in this cathode stream; that emitted by ordinary soda glass is of an emerald green colour, while the fluorescence from lead or lithium glass is blue.

The cathode rays were discovered by Plücker in 1859. Crookes, as a result of his own experiments about twenty years later, adopted the view that the cathode stream represented a fourth state of matter, as opposed to the view of many other physicists, that it was some kind of disturbance in the ether akin to light.

The discoverer of the cathode rays had shown that they could be deflected by a magnet, and as early as 1890 Schuster had demonstrated that the cathode stream consists of electrified particles, and he measured the deflection which they suffered when influenced by magnetic fields of known strength.

Perrin showed in 1895 that these particles carried a charge of negative electricity, but it was reserved for J. J. Thomson (1897-8) to establish the velocity of propagation of the cathode stream, and the ratio of the mass (m) of the individual particles to the electrical charge (e) that each carried. This he effected by a series of measurements of the deflections produced upon it by magnetic and electric fields of known strength. These observations are of fundamental importance, since from work upon electrolysis the ratio in question is known for the atoms of many of the elements.

The individual particles of the cathode stream are known as electrons, a name given to the unit quantity of electricity by Johnstone Stoney, and they are believed to consist solely of negative electricity.

Subsequent results by J. J. Thomson showed that the individual particles of the cathode stream have a mass of about one-two-thousandth of that of a hydrogen atom, and that each of them carries an electrical charge equal to that of the hydrogen atom during electrolysis, but of the opposite sign, namely negative.

The velocity of this stream of negatively charged particles is found to vary with the circumstances of the discharge through the tube. For any given tube it may be said to vary directly with the square root of the voltage between the terminals, and inversely as the gas pressure inside the tube. Velocities higher than 2×10^{10} cms. per second have been measured for these particles; this velocity is a little more than two-thirds of that of light.

Although cathode particles may be travelling with a very high velocity, they are easily stopped by obstacles placed in their path. Lenard was able to show, however, by making a small window in the glass bulb in which the cathode stream was generated and covering it with a sheet of very thin aluminium, that when the cathode stream was directed on to this window, a type of radiation could be detected outside, which had many of the characteristics of the original stream, for it could be deflected by magnetic and electrical fields, and it produced phosphorescence upon bodies placed in its path. The phenomenon of prime importance is that when such rapidly moving cathode particles are stopped, X rays are produced.

The discovery of this new type of radiation was made by Röntgen two years before the real nature of the particles constituting the cathode stream was made by J. J. Thomson.

These rays differ in many respects from the cathode stream which produces them. They are not deviated from their rectilinear path by either magnetic or electric fields of great intensity, and their power of penetrating matter is much greater than that of the cathode stream responsible for their production. In fact, this characteristic is the one which led to their discovery, for substances, ordinarily opaque to light, such as black paper, wood, etc., were found to be quite easily penetrated by this new type of radiation.

It is now known that X rays are disturbances in the ether akin to light, but their wave-length is very much smaller; roughly speaking, we may say that their wave-length is about ten thousand times less than that of the disturbances known as light.

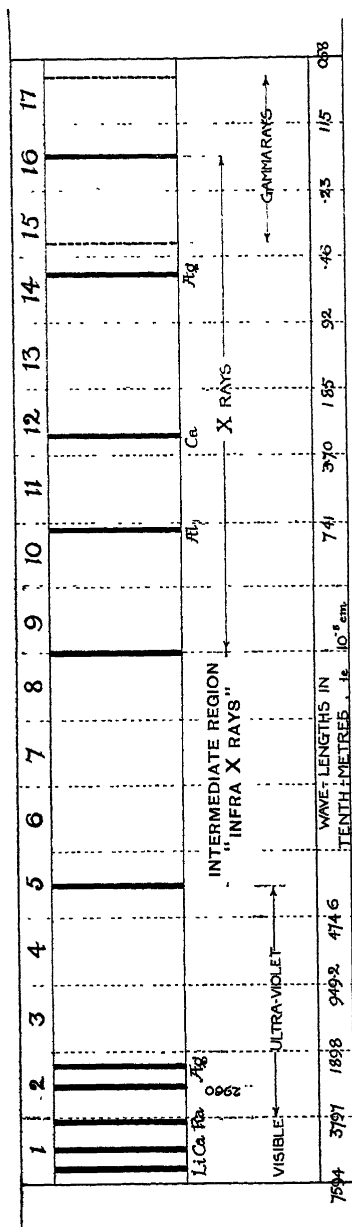


Fig. 2A. Octaves of Electromagnetic Disturbances.

In Fig. 2A are charted the wave-lengths of ether vibrations beginning with visible rays; human vision fails if the wave-length is shorter than 3797 tenth-metres, *i.e.* 3797×10^{-8} cms. Radiations just beyond this are known as ultra-violet rays, they extend over several octaves. At the line marked 2960 pronounced germicidal action begins; at the fifth octave, a region only recently explored begins; the tenth octave we may recognise as the one at which well-recognised X rays make their appearance, though it should be mentioned that X rays of much longer wave-lengths than these have been produced; little is known of their properties, however, except that they are very easily absorbed by matter. It is not until nearly the fourteenth octave is reached that we come to the X rays which are in common use and indeed of chief medical interest; they extend over about three octaves; overlapping them at the fifteenth octave are the gamma rays from radio-active substances, which extend about an octave beyond the most

penetrating X rays yet produced ; to the latter we may ascribe a wave-length of $.122 \times 10^{-8}$ cm., whereas the determinations of Rutherford and Andrade, *vide* p. 58, indicate a value of $.071 \times 10^{-8}$ cm. for the wave-length of the most penetrating gamma rays from Radium *C*.

METHOD OF PRODUCTION OF X RAYS.

X rays are formed when the cathode stream is suddenly brought to rest. This stream is only formed at low-gas pressures, so that the essential feature of an apparatus which will produce X rays is a vessel containing a gas at low pressure, provided with two metallic terminals, which may be connected to some high potential source. The cathode stream leaves the cathode at right angles to its surface ; hence, by making this surface concave and placing the anode at its centre of curvature, the stream of electrified particles is brought to a focus at the anode ; this is a very important consideration in radiographic work where sharpness of shadow outlines is required.

The developments from the earliest X-ray bulbs have been very considerable. Fig. 2 shows a modern focus bulb, and an early

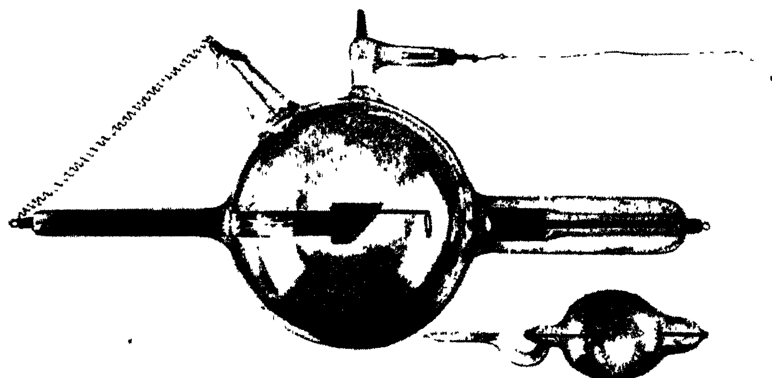


Fig. 2.

tube used for medical work. The bulb is initially exhausted to a pressure of about .01 mm. of mercury, and then sealed off. The anode generally consists of a disk of copper faced with platinum

or tungsten, placed in the middle of the bulb and at an angle of 45° to the line joining it to the cathode. When the cathode stream strikes the anode, the X rays come out practically uniformly in every direction from it. Owing to the fluorescence which they excite upon the glass, the limitation of the X rays to a hemispherical portion of the bulb is easily observed, and is an immediate indicator as to whether the discharge is in the right direction.

The usual high potential source is an induction coil driven from the mains, an electrostatic machine of the Wimshurst type, or some form of interrupterless high-tension transformer.

The current passing through an X-ray bulb, such as described above, is rarely more than a few milliamperes, and may be measured by inserting a milliammeter of suitable type in the bulb circuit; the current passing through the bulb, however, bears no simple relation to the output of X rays from it. For photographic work, bulbs are now made to carry much larger currents (up to 1 ampere), thus enabling the operator to cut down the exposures to considerably less than a second.

THE CANAL RAYS.

If the cathode of an X-ray bulb be perforated, luminous streamers may be observed behind it. These streamers are found to consist mainly of positively charged particles, generally of the gas remaining in the partially exhausted bulb. They are usually atomic particles, which have been driven by the electrical field in between the anode and cathode, so as to go in the opposite direction to the cathode stream; although normally stopping at the cathode, their high velocity carries them through the perforations. They were discovered by Goldstein, who found them to be positively charged, though later investigations by J. J. Thomson showed that in some cases their charge is negative. They are, however, always found to be atoms or molecules of the containing gas, and hence form a type of radiation essentially different from those so far considered.

The recent researches of Aston upon these positive rays have proved beyond doubt that atoms of the same chemical element may differ appreciably in atomic weight.

PROPERTIES OF X RAYS.

The X rays are not visible to the naked eye. The three chief physical indicators of their presence are their photographic action, their power of causing many bodies to fluoresce, and their ionising power, *i.e.* their capacity of producing ions in substances (*vide* p. 8). Their biological effects will be considered in another section, but it cannot be said that these have received as yet any adequate physical explanation.

PHOTOGRAPHIC ACTION.

A solid body such as a coin laid upon a photographic plate exposed to the X rays, screens the plate to some extent from their action, the resulting negative giving evidence of the coin by the shadow it casts. The depth of this shadow depends upon the density and thickness of the material used. For a given thickness of material the depth of shadow depends upon the density of the substance interposed. As a consequence of this, a radiograph reveals the bony structure of the hand, the absorption of the rays by the bone being greater than that by the less dense fleshy parts.

In radiographs of the human body, the ease with which recognition of adjacent organs may be made depends not only on their own particular absorption of the rays, but also upon the different extent to which superimposed organs have exercised this same capacity.

The difficulty of obtaining sufficient contrast in radiographs of parts of the body of approximately the same absorptive power has to a certain extent been overcome by imposing an artificial density upon one part, which part then exerts a greater absorption upon the rays than it otherwise would. By the introduction of bismuth or barium compounds into the stomach, some extraordinary developments in its examination have of late years been made. The whole intestinal tract and sinuses, the ureter and kidneys, have also been mapped out by similar methods.

FLUORESCENCE.

Many substances fluoresce under the action of X rays. The X rays proceeding from the anode of an ordinary bulb, in their

passage through the glass, cause it to fluoresce with a greenish yellow light, the precise tint depending upon the character of the rays. The gas in the bulb plays some part in the phenomenon.

The double cyanide of barium and platinum fluoresces brilliantly under the action of the rays, so much so that a screen of this material held behind the object irradiated allows the picture to be seen before it is photographed.

This is, of course, an invaluable aid in radiographic work, but there is a lack of the finer detail in the fluorescent screen picture when compared with the photographic negatives.

Fluorescent screens of calcium tungstate placed over the photographic plate are sometimes used to increase the rapidity of the photographic action of X rays. The light emitted by the calcium tungstate is rich in violet and ultra-violet rays, which have marked photographic action.

IONISATION.

Many substances known as dielectrics, which are normally bad conductors of electricity, have appreciable electrical conductivity conferred upon them when subjected to X radiation. Thus X rays in their passage through air, which ordinarily conducts electricity to an almost inappreciable extent, confer upon it a degree of conductivity which is very easily measured by means of an ordinary gold-leaf electroscope. The air is said to be ionised during the passage of the X rays through it.

Our knowledge of the way in which this is effected is somewhat hypothetical, but from the results of observations which have been made on numerous gases at different pressures when subjected to X rays, it seems that the process of ionisation in gases consists in the sudden liberation of one or more electrons from a molecule; the electron, carrying away a negative electrical charge, leaves the remainder of the molecule positively charged. This condition of things is but momentary, for the liberated electron quickly becomes the nucleus of a cluster of uncharged molecules which form around it, which also happens in the case of the positively charged particle. The result is that positively and negatively charged clusters of molecules are formed in the gas in equal numbers, and these are what are understood as

gaseous ions. When the pressure of the ionised gas is reduced, the clusters are not formed, and the negative ion probably then exists simply as a free electron.

The way in which electrical conductivity is produced in a gas is therefore easily pictured, and the process of the discharge of electricity from a charged body receives a ready explanation. If the gold leaves of an electroscope are charged positively, the walls of the containing vessel will be negatively charged. The extent of the divergence of the leaves is a measure of the electrical charge upon them, and if the air within the electroscope is now ionised, the negative ions are attracted to the positively charged leaves, the charge on which is gradually neutralised, as a result of which the leaves tend to fall together ; the opposite charge on the walls of the vessel is simultaneously neutralised.

The ionising action of X rays is exceedingly powerful, and is moreover, one which lends itself to exact measurement.

Solid and liquid dielectrics are also rendered conducting to a slight extent by the action of X rays. During the radiation of any tissue, a local increase in the ionic content of the permeating fluids may occur ; owing to their normally high conductivity, it would be difficult to detect any such change in strong electrolytes, but in the case of the constituents of a colloid nature it will be seen in a following section that important changes occur in them under the action of X rays, as well as the rays from radioactive substances.

THE MEASUREMENT OF IONISATION.

Mention will frequently be made of the ionisation caused by the different types of radiation with which we are here concerned, and the following considerations in connection with measurements of gaseous ionisation are of importance.

Consider a beam of X rays, which is allowed to enter a metal box (Fig. 3) through a small aperture *W*, covered over with a thin leaf of aluminium which does not appreciably absorb the rays. The box is provided with two metal plates, *C* and *D*, which are connected to the two poles of a battery of cells, in circuit with which is a measuring instrument of some kind ; in the case depicted, an electrometer. Before allowing the rays to enter the box, the air between the plates is such a bad conductor

of electricity that practically no current is recorded by the instrument, although the voltage between the plates be several hundred volts.

Immediately the X rays are allowed to enter the box, the air becomes ionised, and, in consequence of the electric field, the

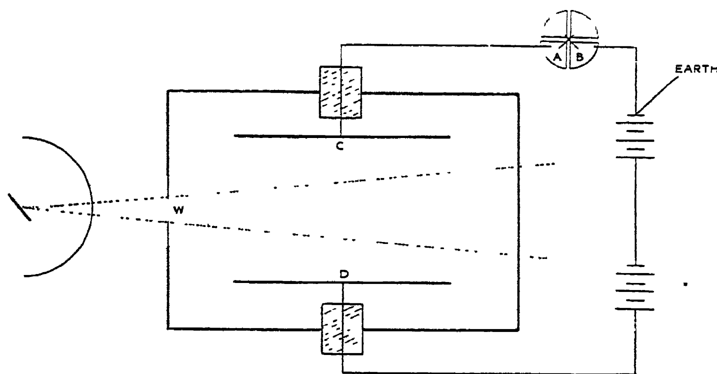


Fig. 3.

ions are attracted to the two plates, the positive ions to the negative plate and the negative ions to the positive plate. The transport of these ions constitutes the electric current, which is measured by the instrument in circuit. It is found that the current increases with the voltage, *i.e.* the difference of potential between the plates, until a voltage is reached at which the current remains steady, and this value is known as the "saturation current"; the meaning of this is that the ions are removed from the gas at the same rate as they are being formed, hence an increase in the voltage causes no augmentation of the current. With smaller voltages than this saturation voltage, a number of the ions re-combine with one another before reaching the electrodes, and consequently the actual current measured is diminished.

When accurate measurements are required, care must be taken to obtain the saturation current; this can generally be assured by having a high voltage acting between the two boundaries of the system. Similar considerations apply when a gold-leaf electroscope is used to measure the ionisation current in a gas.

HARD AND SOFT X RAYS.

The character of the X rays emitted from a bulb depends upon the pressure of the gas within the bulb, and the difference of potential (or number of volts) between the anode and cathode. This is because the character of X rays depends on the velocity of the cathode particles exciting them, and the velocity of the cathode particles in turn depends on the electric force driving them from the cathode to the anode. When the gas pressure is gradually reduced, the cathode particles travel more quickly, even though the voltage remains constant.

If a bulb is started with the gas pressure not very low, the type of radiation is "soft," by which is meant that the rays will not penetrate matter very readily, and are therefore easily absorbed by substances placed in their path. As the bulb continues running, the vacuum generally improves and the rays get "harder," *i.e.* they have greater penetrating power. The radiation coming away from the bulb is, however, always of a heterogeneous character; and when a bulb is said to be running "soft," it means that in the main the rays are easily absorbed, but there will still be a considerable percentage of more penetrating rays under such circumstances. In the same way a "hard" bulb will not only provide highly penetrating rays, but simultaneously a varying proportion of "soft" and "medium" rays.

It is rather remarkable that a comparatively simple relationship holds between the voltage applied to the terminals of an X-ray bulb and the velocity of the cathode stream; as already stated, this velocity varies as the square root of the voltage. Further, it has been shown that when electrons move under comparatively small voltages the X rays to which they give rise are of comparatively long wave-length and have small penetrating power; as the voltage is increased, the velocity of the electrons increases, and the wave-length of the X rays to which they give rise on being stopped is shortened, the penetrating power increasing simultaneously; with still further increased voltage the speed of the electrons may almost reach that of the velocity of light, and such high-speed electrons produce X rays of still shorter wave-length, with much augmented penetrating power.

J. J. Thomson showed that on theoretical grounds the energy of a beam of X rays should increase as its wave-length is decreased, and his prediction that it should vary as the fourth power of the applied voltage has been substantiated. Hence it is useful to bear in mind that the more penetrating the X ray is the more energy is associated with it; in many cases, however, the less penetrating types of X rays give rise to more pronounced effects than do those of shorter wave-length; this is generally due to the fact that although they possess less energy it is more easily liberated on meeting any obstacle in their path. It is a natural enquiry to find what relation exists between the wave-length of the X rays and their penetrating power through various substances. Here in general it must be said that no very simple relation exists, owing to various processes of a secondary nature occurring when X rays strike an obstacle. Nevertheless, if attention be restricted to a substance like aluminium, the absorbing power varies in a fairly simple way with the wave-length of the X rays. If the wave-length is doubled, the absorption which a sheet of aluminium would exert upon the beam would be increased about six-fold; this matter is referred to again, *vide* Tables 4 and 9.

The changes occurring in the radiation from a bulb when in action are in many cases very undesirable, and are to a certain extent counteracted by the device *D* seen in Fig. 2, which consists of a disk coated with powdered talc. As the vacuum improves, a spark passes from *A* to *C*, with the consequent liberation of a small amount of occluded gas from *D*, which tends to maintain the gas pressure. By fixing the distance that the spark has to discharge through, the character of the discharge may be maintained the same for considerable periods.

Many devices have been made for this automatic regulation of the spark distance. One of the most important requirements is that such a device should not necessitate the operator being near the bulb, owing to the dangers of exposing the body to the rays. A great advance has been made by Coolidge in producing an X-ray bulb, the radiation from which is capable of accurate adjustment by the operator. The principle underlying the working of the bulb differs from that of the ordinary gas tube in an important particular: the bulb is freed of air as

completely as possible by mechanical means, and under these conditions no discharge will pass from an ordinary cathode to the anode. Coolidge has made use of the well-known fact that when certain metals are heated to a very high temperature they emit electrons; these electrons form the cathode stream in the Coolidge tube. The cathode *C* (Fig. 4) consists of a small flat spiral of tungsten which is heated by a current of 4-5 amperes; this provides a copious stream of electrons. When the requisite voltage is applied between the terminals of the bulb, these electrons are accelerated towards the anode, where the X rays are formed. The penetrating power of the rays depends only upon the voltage applied at the terminals; and, once adjusted to any particular value, the radiation is not subject to any of the undesirable changes referred to. The consideration of the general features of the radiation from such a bulb is dealt with in Chap. III.

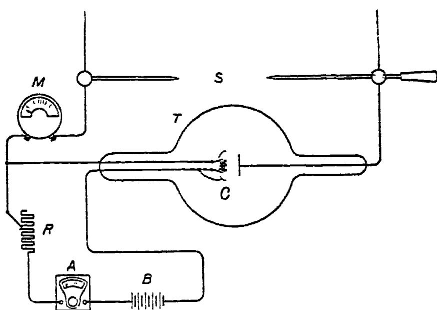


FIG. 4.—Coolidge X-Ray Tube. The cathode stream originates from *C*, a flat spiral of wire heated by a current from the battery *B*

THE MEASUREMENT OF X RAYS.

The most accurate method by which the intensity and character of X rays can be measured is by the ionisation that they produce.

It seems likely that this method will receive wider clinical acceptance as the necessity for more accurate dosage increases, but there are great experimental difficulties to be overcome before the ionisation method can come into general use.

One of the first units of X-ray intensity used for clinical purposes was introduced by Holzknecht. He prepared a pastille which, under the action of the rays, gradually changes in colour from a canary yellow to brown. He prepared a scale graduated for intermediate tints, which was numbered 1–20. The unit on this scale is the amount of radiation required to change the colour of the pastille from one shade to the next, this unit being denoted as 1 H.

Sabouraud has prepared a similar pastille; when it is placed at a distance from the anode and changes to the colour of a standard brown, the radiation received by a surface at twice this distance is said to be one pastille dose.

Although these pastilles are in extensive use among radiologists, there are few who will claim that their indications are a satisfactory guide to the dose of X rays which the tissues of the body may be receiving.

We have seen that a bulb may vary in its behaviour in two important particulars. The intensity of the radiation varies with the current passing through the bulb, while the character of the radiation depends upon the voltage applied to the terminals.

A simple experiment may show the misleading indications of these pastilles. A pastille is placed in the usual position and exposed to the rays from a very "soft" bulb, and the time noted to change its colour to the standard tint; the bulb is then hardened and the current in the primary of the induction coil adjusted, so that a new pastille placed in position suffers the same colour change in the same time. The dose, as measured by these two pastilles, is the same, yet the clinical effects upon the tissues are profoundly different in the two cases.

The Kienböck method is a photographic one; strips of photographic paper are exposed to the X rays for a short interval, and then developed under standard conditions; the resulting tint of the paper is then compared with a standard tint, and the quantity of X rays deduced from the result of such comparison.

The action of the Furstenau Intensimeter depends upon the fact that the resistance of selenium changes when exposed to X rays. A selenium cell is made the fourth arm of a Wheatstone bridge, the balance of which is upset when the cell is exposed to the beam of X rays. The extent to which this occurs depends upon the intensity of the beam of X rays, and is measured by a direct reading galvanometer. The Bordier unit depends upon the chemical action of the X rays; when exposed to X rays, iodine is liberated from a solution of iodoform in chloroform. Bordier found that the quantity liberated was directly proportional to the exposure to the rays; he has adopted a colorimetric method of determining the amount of iodine liberated, and as an X-ray unit for therapeutic purposes, he takes that quantity

of rays which liberates .1 milligram of iodine in 1 c.c. of a 2 per cent. solution of iodoform in chloroform.

TABLE I.

COMPARISON BETWEEN THE VARIOUS UNITS USED IN MEASURING THE QUANTITY OF X RAYS

Sabouraud-Noiré Radiometer.	Holzknecht Chrano-radiometer.	Kienbock Quantito-meter.	Bordier Quantimeter.	Furstenau Intensimeter.
Tint B	1 H 5 H 20 H	2 X 10 X 40 X	Independent Unit	60–80 Units Soft X rays

By the term "character" is meant the degree of penetrating power of a beam of X rays. Under the ordinary conditions of production, the beam is heterogeneous, *i.e.* it consists of a number of rays of different wave-lengths. What determines the composition of this mixture of rays is the potential difference between the terminals of the X-ray tube; it is usual to say that, when a comparatively small voltage is employed, for instance 80,000 volts, the radiation is of the "soft" type, by which is meant that the major part of the radiation consists of long wave-lengths which are easily absorbed by the tissues or by metallic filters. With very high voltages, such as 200,000, the radiation is frequently referred to as "hard," *i.e.* of a very penetrating character, the average wave-length in this case being shorter than in the first instance. In both of the cases cited, however, there would be present other wave-lengths than the dominant ones to which the terms used apply. A knowledge of the potential difference applied to the tube, if it were constant, should suffice to determine the character of the X rays emitted from it. The degree to which these heterogeneous beams of X rays are absorbed by aluminium has been found by a number of investigators. Instead of actually measuring the potential difference, it is usual to express this in terms of the length of the spark-gap across which the discharge would take place; this is referred to as the equivalent spark-gap.

TABLE 2.

Alternative spark-gap distance in cms. point to point	Potential difference Volts	Bauer Scale	Benoist Scale.	Wehnelt Scale.
3	34,000	2.2	2.2	4.3
4	42,000	2.7	2.7	4.8
6	55,000	3	3	5
8	66,000	3.5	3.5	5.5
10	76,000	4	4	6
15	102,000	5	5	6.8
20	122,000	6	6	7.6
30	170,000	8.5	8.5	9.6
40	220,000	—	—	—

In practice use is made to some extent of penetrometers, which take various forms. The Bauer type of instrument is really an electrostatic voltmeter, although the graduations of the instrument are not in volts, but read from 2 to 10, the higher the number the greater the potential difference and the greater the penetrating power of the radiation. The Benoist and Wehnelt penetrometers depend for their action upon the difference in the ratio of penetrability of two different metals as the character of the X rays is changed; they are useful when it is desired to have upon a radiographic plate a permanent record of the character of the rays; this can generally be done by placing the penetrometer upon a corner of the plate and obtaining a photographic impression of it by means of the X rays used.

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CHAPTER II

SECONDARY X RAYS

WHEN X rays are stopped by interposing some substance such as a sheet of metal in their path, phenomena of great importance occur. Sagnac discovered that from the region of the plate upon which the primary beam of X rays is incident there originate other rays, which are known as Secondary X rays.

Kaye in 1908 showed that the character of the X rays emitted from a bulb depended not only upon the potential difference between the terminals, but also upon the nature of the metal used for the anti-cathode. He found that, in general, there were two types of X rays given out by any anti-cathode, a heterogeneous bundle of rays of various wave-lengths and a homogeneous type of X rays characteristic of the particular metal of which the anti-cathode was made.

Much light has been shed on the difficult subject of secondary radiation by Barkla and Sadler, who have shown that when X rays strike an element of greater atomic weight than aluminium (atomic weight $=27$) there occur :

(1) The production of a *homogeneous* X radiation which is characteristic of the particular element struck.

(2) A certain amount of scattering of the primary beam.

(3) The liberation of cathode particles similar to those occurring in the cathode stream.

The term secondary rays, which is very widely used, comprises the two varieties (1) and (2), though a careful distinction must be made between them. It is safe to say that a primary beam always suffers some scattering on meeting anything in its path, but it is only under certain conditions that " homogeneous " characteristic X rays are produced.

It is found that the primary beam is always of greater penetrating power than the characteristic beam to which it gives rise, and that the intensity of these secondary rays produced is directly proportional to the intensity of the primary beam.

There is thus a partial transformation of one type of X ray into another, effected by the substance which is penetrated.

The "soft" elements of the beam become quickly absorbed. the "medium" and "hard" rays suffer a modified absorption, and simultaneously provoke a softer radiation from the material which they penetrate; this in turn may give rise to an easily absorbed cathode radiation. These secondary phenomena attendant upon the passage of a primary beam are probably responsible for the clinical effects manifested.

In some cases it has been found that more than one beam of homogeneous rays may be excited by a primary beam in the same substance. For instance, the homogeneous secondary rays from silver consist of two beams, one very much softer than the other, the former being half absorbed by about $\frac{1}{300}$th of a millimetre of aluminium, while the latter requires a thickness of 1 mm. to effect a similar absorption.

TABLE 3.—ABSORBABILITY OF HOMOGENEOUS SECONDARY X RAYS.

Element.	Thickness of Aluminium to absorb one half.		Thickness of Water to absorb one half (numbers approximate)	
	Series K.	Series L.	Series K.	Series L
	Millimetre	Millimetre.	Millimetre.	Millimetre.
Calcium - - -	.006		.08	
Iron - - - -	.028		.4	
Copper - - -	.052		.7	
Selenium - - -	.13		2.0	
Strontium - - -	27		4.0	
Silver - - -	1.0	.0036	14	.05
Antimony - - -	2 1	.006	30	.08
Barium - - -	3.0	.01	45	.15
Cerium - - -	4 0		60	-
Gold - - - -		.10		1.5
Bismuth - - -		.13		2.0

The above table shows the penetrating power of the homogeneous secondary X rays which certain elements emit when subjected to a suitable primary beam.

The penetrating power is shown by the thickness of water which is required to cut down the intensity of the beam to one half of its original value. Water has been chosen as approximating fairly closely to the average density of the tissues of

the body. The experimental results are due to Barkla, who designated the two types of rays by the letters K and L.

The tissues of the body consist for the most part of substances which contain the light elements, hydrogen, carbon, nitrogen, and oxygen. Now it is just these and others of the light elements from which homogeneous secondary X rays have not yet been obtained, but which exert some scattering action upon a primary beam. If there are such homogeneous rays, it is probable that they are of a very " soft " type.

The ionising action of the X rays is one of their most striking features, and occurs in liquids as well as in gases ; but how far the biological effects are the result of such ionisation remains for subsequent work to decide. Now that some of the fundamental properties of secondary X rays are known, it is highly probable that efforts may be directed towards their use.

THE DISTRIBUTION OF SECONDARY AND SCATTERED X RAYS.

If a thin copper plate be interposed in the path of a suitable primary beam of X rays, we have seen that there originates at the metal plate a secondary type of X rays.

Barkla has shown in the above case that the intensity of such radiation is uniform in every direction, and in fact that just as much comes back from the plate as proceeds in the direction of the primary beam.

The purely scattered radiation is always of the same type as the primary beam ; in cases where a substance gives out a characteristic secondary radiation it is of little importance. But for substances like carbon and aluminium, which give little, if any characteristic secondary radiation, it is of greater significance.

For carbon, Barkla has shown that the symmetry of its distribution is not so complete as in the case of the radiation from copper which has been considered, less being scattered normally to the direction of the primary beam than in other directions. In the case of aluminium, Crowther has shown that less is scattered back from the plate than in the direction of the primary beam.

The different behaviour of the light and heavy elements in partially scattering an incident beam of X rays is of interest

in its bearing upon the definition obtained in radiographs. The relative scattering of soft and hard rays by the various organs may very well be a matter for consideration in the selection of the most suitable type of rays for a particular radiograph.

THE INTENSITY OF HOMOGENEOUS SECONDARY X RAYS.

From what has already been stated, a little consideration will show that, whether the intensity of the secondary beam of X rays compares favourably with that of the primary depends entirely on the character of the primary beam and the nature of the substance used for the production of the secondary.

To take a concrete case, let us suppose that the primary beam was of an average hardness corresponding to that of the characteristic radiation from zinc, and a soft homogeneous beam were required. Iron would in this case be a suitable metal to use, for it exerts a " selective absorption " upon rays of the hardness in question, effecting their conversion into a type which would be about 2.25 times as soft as the original beam.

Measurements of the relative intensity of the two beams is complicated by the fact that the ionisation depends upon the hardness of the rays, but from some experiments upon homogeneous primary beams, Barkla was led to the view that the intensity of the secondary radiation may be a considerable percentage of that of the primary.

He has shown that at its maximum the homogeneous secondary radiation from copper accounts for about one-third of the energy of the part of the primary beam *that is absorbed,* and that it is a hundred times as large as the purely scattered radiation—the relative energies being measured by the ionisation power of the different radiations.

It will be noticed that the fraction $\frac{1}{3}$ refers only to that part of the primary radiation which is absorbed by the copper, and it is practically certain that this fraction must decrease as the thickness of the copper radiator is increased in order to absorb more and more of the primary rays.

It is not always recognised that in applying the results of such energy measurements to different experimental arrangements a possible fallacy is encountered. Suppose, for instance, that the intensity of a primary beam is measured by the ionisation it

produces in the air contained in an electroscope, and found to be 100 of some arbitrary units. Now suppose that a copper radiator intercepts the primary beam, and that the ionisation it produces in the air of a symmetrically placed electroscope, shielded from the primary beam, is measured and found to be 10 of the same units. Then, although the ionising action of the secondary rays upon air may be 10 per cent. of that of the primary, it would be quite unjustifiable to assume that such a percentage could serve as a therapeutic measure of the secondary radiations, for, as will be seen from Table 3, the copper radiation would be half absorbed in going through a layer of tissue .7 mm. thick, whereas the primary radiation exciting it might be of such penetration as to considerably affect the deeper tissues not even reached by the softer radiation from the copper.

It has to be remembered that electroscopic measurements upon X rays are in nearly every case measurements of the *intensity* of the rays and not of their *energy*. Under the usual conditions a minute fraction of the energy of the beam of X rays is utilised in causing ionisation of the air or gas in the containing vessel.

The clinical use of homogeneous secondary rays would in many cases entail a large increase in the time of exposure, but whether this will militate against their use, which seems desirable on some other grounds, remains to be seen.

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CHAPTER III

THE TRANSMISSION OF X RAYS THROUGH MATTER

In view of the secondary phenomena attendant upon the passage of X rays through matter, it is clear that few accurate statements can be made as to the transmission of X rays through a substance without these secondary phenomena being taken into consideration.

We have seen that if the characteristic secondary X rays are to be provoked in an elementary substance, the primary rays must be more penetrating than the secondary rays. It has been found that substances exert a "selective absorption" on rays which are considerably harder than their own characteristic rays. For instance, iron absorbs the characteristic radiation from copper (which is *harder* than its own) about $2\frac{1}{2}$ times more powerfully than the characteristic radiation from chromium, which is *softer* than its own. We have thus the apparently anomalous condition that a *hard* beam may be more *easily* absorbed than a *soft* one, if the character and nature of rays and absorbers are appropriately chosen.

The main issue to be decided is, what has been done to a primary beam of X rays on interposing a sheet of some substance in its path? In what way have its intensity and character been altered?

The primary beam being usually heterogeneous, it is clear that a numerous variety of cases would have to be considered before a reply could be given to these questions.

In lieu of this it may be useful to consider three typical cases which have been examined by Barkla and Sadler, in which the primary beam is homogeneous:

1. When a homogeneous beam passes through a plate of some

element whose characteristic radiation is of equal or greater penetrating power, the characteristic radiation is not provoked and the transmitted radiation remains unaltered in character, but diminished in intensity, owing to absorption and scattering throughout the plate.

2. When a homogeneous beam passes through a plate of some element whose characteristic radiation is of a more absorbable type, and more absorbed *in the plate itself* than the incident beam, the transmitted radiation retains some of its characteristics, but has now added to it a softer type of radiation.

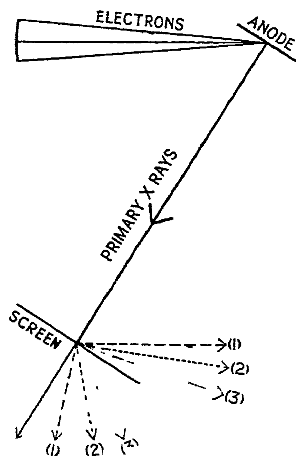


FIG. 5.

3. When a homogeneous beam passes through a plate of some element whose characteristic radiation is of a more absorbable type, but more penetrating *through the plate* itself than the incident beam, the radiation transmitted through a sufficiently thick plate may now consist of a softer type of radiation than the primary beam.

On many occasions it is desirable to eliminate the soft rays contained in a primary beam of X rays, and it may be seen from the above consideration that unless a proper selection of screens be made, some soft radiation may actually be introduced in the act of screening.

Barkla was unable to find any secondary rays from aluminium, but Whiddington has detected a very soft type of secondary rays from it, which he considers characteristic.

Aluminium is often used clinically for screening purposes, but in view of this secondary radiation and of the possibility of other metallic impurities being present and giving out their secondary rays, it seems desirable that only non-metallic screens, such as paper, leather, felt, etc., should be used.

The sequence of changes occurring in the passage of X rays through matter may be represented by Fig. 5.

The cathode particles strike the anode and cause the formation of primary X rays. These, on meeting a metallic screen *B*, are partially scattered (1), they also give rise to secondary homo-

geneous X rays (2) and to secondary cathode particles (3), all of which may be detected on either side of the screen.

In reality, the rays proceed in every direction from the screen *B*, but for clearness in the drawing they are limited to some arbitrary direction.

The secondary X rays and cathode particles in turn provoke other disturbances of a similar nature as they pass through the surrounding medium, but the above indications will suffice to give some idea of the phenomena to which the initial cathode stream may give rise.

The clinical significance of secondary X rays will be appreciated when we consider what happens as a heterogeneous beam of X rays penetrates the body.

The whole sequence of phenomena is doubtless very complicated, but if, as seems likely, we may think of the beam as having no effect upon the medium through which it is passing, unless it is absorbed, or transformed to some extent by the medium, then at each successive stage of its passage through layers of tissue these processes are the ones which require consideration.

Since the tissues of the body differ from one another in their chemical constituents to a very large degree, both in their organic and mineral content, the transformations of a primary beam of X rays in its passage through the tissues will be different in character according to the variety of tissue met. It is very probable that the mineral content would be mainly responsible for the production of "characteristic rays" and the organic portions for the scattering of the primary beam; both processes in their turn giving rise eventually to secondary cathode particles which dissipate their energy in the tissues.

The quantitative estimation of the absorption suffered by a beam of X rays in its passage through a substance may be made by measuring the ionisation caused by the beam initially, and tracing the gradual diminution in this ionisation as successive layers of the material in question are interposed between the beam and the ionisation vessel.

The criterion for the homogeneity of X rays is that they are absorbed according to an exponential law. The ionisation will have a certain value corresponding to any thickness of matter traversed by the rays. When the logarithms of the values of the

ionisation are plotted as ordinates, and the thickness of matter traversed as abscissae, the points on the diagram will lie on a straight line if the absorption of the rays has followed an exponential law. This test, when applied to the radiation from an X-ray bulb, reveals the heterogeneous character of the rays, as may be seen from the curves in Fig. 6.

Two typical cases are represented. Curve I. illustrates the way in which the rays from a "soft" bulb (spark gap of about 10 cms. between points) are absorbed by interposed screens of aluminium. Curve II. illustrates the same thing for very "hard" X rays (spark gap of about 30 cms. between points), all of the softer components being cut out by 7 mm. of aluminium. If curve I. be analysed in the manner suggested above, the logarithms of the ionisation will be found not to lie upon a straight line, but the curve may be arbitrarily divided into three sections, *D*, *E* and *F*, over which the radiation is practically of one degree of hardness, and numerical values may be apportioned to them for purposes of comparison. Although nominally a "soft" bulb, analysis shows that the radiation is heterogeneous, consisting of "soft" rays (portion *D*), medium rays (*E*), and hard rays (*F*). When a similar analysis is made of curve II., the radiation is found to be practically homogeneous and of a "very hard" character. Numerical values will be found in Table 4.

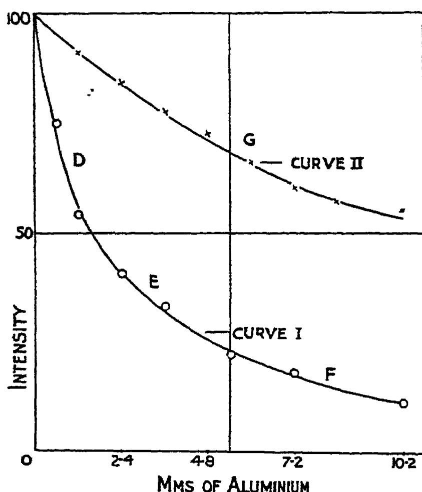


FIG. 6.

THE COEFFICIENT OF ABSORPTION OF THE RAYS.

It is convenient to refer to the penetrating power of a beam of rays in terms of a coefficient * (λ), the numerical value of which

* The value of λ is obtained as follows: The intensity of a homogeneous beam in its passage through matter may be represented by the equation:

$$I = I_0 e^{-\lambda d},$$

is inversely proportional to the penetrating power of the beam. A large value of λ corresponds to an easily absorbed beam, and a small value to a very penetrating one. The value of λ also varies according to the nature of the absorbing material.

If after traversing 1 cm. of matter the ionisation in the electroscope is reduced to one-half its initial value, $\lambda = \cdot 69$ cm.$^{-1}$, which is just about the mean value found for the absorption by fatty tissues (breast) of a beam of " soft " X rays.

It is clear that, when dealing with a heterogeneous beam, the value of λ varies with each succeeding layer of matter traversed, because the soft components of the beam will have a large value of λ, the medium components a smaller value, and this will diminish further still for the hardest components. If the beam be homogeneous, the value of λ is constant.

TABLE 4.—VALUES OF THE COEFFICIENT OF ABSORPTION (λ) OF X RAYS IN ALUMINIUM (cm $^{-1}$) AND THEIR WAVE-LENGTHS.

Type of X Rays.	Value of Coefficient of Absorption λ.	Wave-length.
Soft - - -	7.20	5 5 10^{-9} cm.
Medium Soft (D) -	5 10	4.85 ,,
Medium (E) - -	2 14	3.43 ,,
Hard (F) - -	1.34	2.84 ,,
Very Hard (G) -	.66	2.14 ,,

With regard to the penetration of animal tissues by X rays, an extensive series of measurements was made in 1905 by Perthes, who found that the absorption by most of the tissues was extremely near to that of water, the exceptions being lung and fatty tissues, which are lighter than water. Perthes determined the thickness of tissue required to reduce the intensity of the X rays by a certain amount, as measured by a fluorescent screen, and also the thickness of aluminium which produced the same reduction. From the values given in his paper it appears that aluminium is from 7 to 10 times as effective an absorber of X rays

Where I_0 is the initial intensity of the beam and I the intensity after a thickness of matter *d* has been traversed. Hence

$$\lambda = 2.302 \frac{(\log_{10} I_0 - \log_{10} I)}{d}.$$

as tissues of about the same density as water; this is nearly 3 or 4 times as much as its density would suggest.

Guilleminot has made an elaborate study of the absorption of X rays by determining the intensity of the rays after passing through various thicknesses of tissue; this was done for screened as well as for unscreened rays, the data for which may be seen in Table 5.

TABLE 5.

DEPTH OF TISSUE.

Quality of Rays.		Surface.	·5 cm.	1 cm	2 cms.	3 cms.	4 cms	5 cms.	6 cms.	7 cms.	8 cms.
4 Benoist		Dose transmitted, 100	65	43	22	13	8	5 2	3.8	2.6	1.8
5 ,,		,, 100	72	53	32.5	21.9	15 5	11.6	8.8	7 0	5 5
6 ,,		,, 100	78	63	44	33	26	21	17 2	14.4	12
7 ,,		,, 100	81	68	50	39	32	26.5	22.8	19 7	17.2
8 ,,		,, 100	83.2	69.9	52.7	42	34.8	29.5	25.5	22.3	19.6
	Filter.										
8 ,,	1 mm.	,, 100	86 5	76.2	61.1	50 6	43	37 3	32.6	28.5	25 4
8 ,,	2 ,,	,, 100	89 2	80.4	67	57.1	49.4	43.3	38.2	33 8	30 1
8 ,,	3 ,,	,, 100	91	83.5	71.8	61 8	54.5	48 0	42.5	37 8	34 8
8 ,,	4 ,,	,, 100	92.8	86	74.5	65 4	57 8	51.3	45 7	41 0	37
8 ,,	5 ,,	,, 100	95	87	76 1	67 2	60	53 8	48 5	44	40.2

With these data the intensity at any depth of tissue may be calculated, regard also being had to the increase in distance from the anode as greater depths are considered. Scattering has not here been taken into account.

A variety of substances may be used when it is desired to screen a beam of X rays; that is to say, to cut off its softer components. Metal filters are always in radiological practice a potential danger, for we have seen that they are capable of giving rise to secondary rays when a primary beam falls upon them, and these secondary rays are always softer than the primary beam so that, instead of the beam of rays being screened of its soft components, they may actually be augmented by the indiscriminate use of metallic filters.

Salmond has made a comparison of the effectiveness of different screens commonly used. The data obtained by him are collected in Table 6, and represent filtration equivalents; thus .5 mm. of aluminium is equivalent in screening power to 10 mm. of chamois leather, and so on.

TABLE 6.

Aluminium.	Pure Paper.	Tanned Leather.	Chamois Leather	Felt.	Lead Acetate Lint.	Sodium Tungstate Lint.
mm	mm	mm.	mm	mm.	Layers.	Layers.
·5	3	3	10	13	1	2
1–0	7	7	18	30	2	4
2	13	13	35	67	4	8
3	17	16	59	97	6	12

In discussing the gradual absorption by the tissues of X rays of various degrees of hardness, Perthes in 1905 remarks: "It is not known whether in the absorption of the same quantity of 'soft' and 'hard' rays the same physiological effects are produced." In 1911 Belot, in 1912 Spéder, and in 1913 Régaud and Nogier brought forward evidence to show that for the same quantity of "soft" and "hard" rays absorbed by the skin the physiological effects were actually of quite different nature. Testimony of this kind must induce caution in attempting to draw too close an inference as to the action of X rays on the living cell, from physical considerations alone.

The answer has been given by A. W. Porter to the question arising from the following considerations. If a deep-seated lesion is to be irradiated, the question arises as to whether the radiologist should use very "hard" rays in spite of their relative inefficiency as regards ionising action, or "medium" rays, which, although more absorbed by the super-imposed tissues, might be advantageous owing to their greater efficiency. Porter has shown that in order to apply a maximum intensity of rays at a depth d, that particular radiation should be selected which is diminished to one-half of its intensity by this thickness d of tissue.

While the working simplicity of this arrangement strongly commends it, the fact that soft and hard rays when absorbed in equal quantities by the tissues give rise to such different physiological actions has also to be considered by the radiologist in selecting his radiation. It has been mentioned that X rays are ether vibrations, and the rays in medical use range over several octaves of wave-lengths; it becomes less and less likely that questions of expediency will

stand in the way of the selection of the particular wave-length appropriate to the pathological condition which may be under consideration.

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CHAPTER IV

THE NATURE OF X RAYS AND THE IONISATION THEY PRODUCE

X RAYS exhibit many differences from rays of ordinary light. They are not regularly reflected by media in general, and their extraordinary powers of penetration through substances opaque to light bring them into striking contrast with this type of radiation.

Experiments on their velocity have been made by Marx, who found it identical with that of light. His experiments, however, have been subject to considerable criticism by Franck and Pohl, but later determinations by Marx himself confirmed his original findings, and in view of modern developments it is probable that Marx is correct in his original statement.

It has been shown by Stokes that when an electron, moving with the high speed attained in the cathode stream, is started or stopped, an electrical pulse must originate, which has many of the properties of X rays. On this theory the breadth of the pulse varies with the nature of the exciting cathode rays, becoming thinner as the velocity of the latter increases.

With a succession of such pulses directed through the ether, a series of discrete waves may be pictured, the differences among which may be referred to as differences in their wave-length.

Experiments have been made by several observers to determine the wave-lengths of X rays. The earliest experimental results, namely, those of Haga and Windt, based upon certain diffraction effects, indicated a wave-length of about $.1\mu\mu$* for some of the X rays they used. Some observations by Maier yielded a wave-length of $15\mu\mu$. Knowing as we do the wide

* $1\mu\mu$ is equal to 1 millionth of a millimetre.

range of penetrability exhibited by these rays under different experimental conditions, the above differences are not surprising. Both results indicated an order of wave-length far beyond the ultra-violet.

It is not until quite recent times (1912) that the true nature of X rays has been demonstrated. Some experiments initiated by Laue, and carried out by Friedrich and Knipping, have shown that if advantage be taken of the perfectly regular molecular arrangements to be found in many naturally occurring crystals, then it can be shown that X rays consist of ethereal waves and appear to be regularly reflected, just as light may be from ordinary reflecting media.

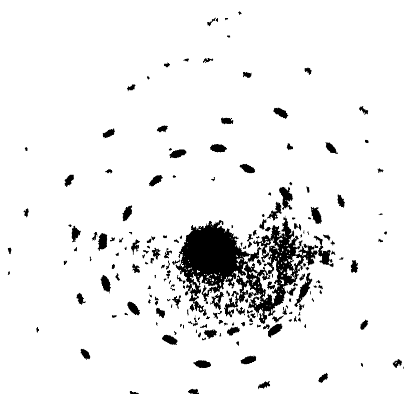
If a beam of homogeneous X rays is incident upon a cleavage plane of a crystal, a certain fraction behaves as if it were reflected in a definite direction by the molecules regularly arranged in the crystal plane, and the remainder of the beam penetrates to the next layer, a fraction again being reflected in the same direction as the first reflected beam.

These two reflected beams may reinforce each other's effects, or they may tend to neutralise each other, and in this way give rise to the phenomenon of interference. From photographic impressions of these reflected beams deductions may be made as to the wave-lengths of the beam of X rays in question.

The development of this line of enquiry in this country has been largely made by W. H. Bragg and W. L. Bragg, and also by Moseley and Darwin. Making certain assumptions as to the distance separating the reflecting planes in a crystal, the wave-length of the reflected X rays may be found. The difficulty lies in deciding whether to take the distance as that between two successive planes or two planes identical in all respects. For instance, there are reasons for believing that the atoms of a cubic crystal, such as rock salt, containing two elements of equal valency, are arranged parallel to one plane, in layers containing equal numbers of sodium and chlorine atoms.

Now, if the distance in question be taken between planes passing through atoms identical in all respects, the resulting wave-length will be just twice that obtained by taking the distance to be that between successive planes.

As an example, W. H. Bragg and W. L. Bragg, in measuring the wave-length of part of the radiation from a platinum anti-



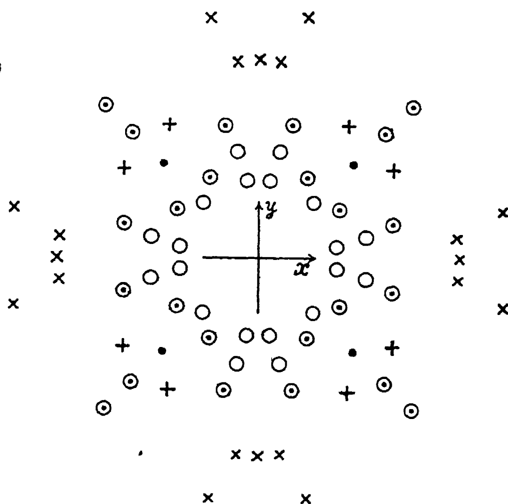


PLATE II.
X-RAY PHOTOGRAPH BY MEANS OF CRYSTAL OF ZINCBLENDE.

cathode, give the wave-length as 1.78×10^{-8} cm. or $.89 \times 10^{-8}$ cm., according as the first or second assumption be made.

The wave-length given above was for a beam reflected from one face of a rock-salt crystal at a glancing angle of 11.55°.

A more correct determination of this radiation by W. H. Bragg resulted in the value 1.10×10^{-8} cm. for the wave-length.

Some further values obtained by this same author are as follows:

TABLE 7.

Anticathode.	Wave-length.	Character.
Nickel -	1.66×10^{-8} cm.	Weak
Tungsten -	1.25×10^{-8} cm.	Weak
Rhodium -	$.607 \times 10^{-8}$ cm.	Very strong
	$.533 \times 10^{-8}$ cm.	Much less intense

The uncertainty referred to has been partly removed by results which W. L. Bragg has obtained on the actual structure of the crystals used for such investigations, for he has shown that if one atom in the molecule is at least twice as heavy as any of the others, it is the lattice formed by these heavy atoms alone which the diffraction pattern reveals; hence in these cases it is the distance between successive planes, identical in all respects, which has to be taken into account.

This method of analysis of Röntgen radiation is of great importance, and to illustrate its advantages over the usual method of determining the character of the radiation from a bulb, namely, that of determining the absorption of the rays by aluminium, we may take the case of an X-ray bulb with platinum anticathode. The ordinary absorption method shows that the radiation from it is heterogeneous to a marked degree, but by the new method of analysis Moseley and Darwin were able to show not only a continuous spectrum corresponding to this heterogeneity, but superimposed upon it there were five distinct types of homogeneous radiation.

The "characteristic" X radiation from various elements has been examined by Moseley by an elegant development of these methods, and in view of the growing importance in biological

studies of these "characteristic" radiations, a few of his data are collected in Table 8.

TABLE 8.

Element	Atomic Weight.	Wave Length.	
		Line A.	Line B
Calcium - -	40 09	3.368×10^{-8} cm.	3.094×10^{-8} cm.
Manganese - -	54.93	$2\ 111 \times 10^{-8}$ cm.	$1\ 918 \times 10^{-8}$ cm.
Iron - - -	55.85	$1\ 946 \times 10^{-8}$ cm.	1.765×10^{-8} cm.
Copper - -	63 57	1.445×10^{-8} cm.	1.402×10^{-8} cm.
Zinc - - -	65 37	1.445×10^{-8} cm.	1.306×10^{-8} cm.

From Barkla's determinations of the absorption coefficients in aluminium of these same characteristic radiations, a comparison may now be effected between the wave-length of X rays and the extent to which they will be absorbed by a substance like aluminium.

The secondary rays, classified by Barkla as the K Series, correspond to the rays for which the wave-lengths are given above. The enhanced accuracy of Moseley's measurements shows that they really consist of two distinct rays. For the purpose of the comparison in question the mean wave-length will be taken.

As an example, we will take Barkla's values for the absorbability of the characteristic K radiation, from calcium, iron and copper, and tabulate with them the corresponding wave-lengths determined by Moseley.

TABLE 9.

Element.	Thickness of Aluminium to absorb one half.	Wave-length.
Calcium - -	.006 mm.	3.231×10^{-8} cm.
Iron - - -	.028 ,,	1.855 ,,
Copper - -	.052 ,,	1.475 ,,

It was shown by Owen in 1912 that the coefficient of absorption in aluminium of these rays varies as $\lambda^{\frac{5}{2}}$, that is, if

the wave-length be doubled, the absorption is not merely doubled, but increased about 5.6 times.

Moseley has made an extensive examination of the wave-lengths of the characteristic X rays emitted by the elements, and for purposes of comparison with the absorption coefficients determined by Barkla of these same rays (K Series), the data are collected in Table 10.

TABLE 10.

Element	Wave-length	Element	Wave-length.
Aluminium -	8.364×10^{-8} cm.	Iron - -	1.946×10^{-8} cm.
Potassium -	3.759 ,,	Copper - -	1.549 ,,
Calcium - -	3.368 ,,	Zinc - -	1.445 ,,
Manganese -	2 111 ,,	Silver - -	.560 ,,

For further data in connection with the wave-lengths of the L Series, Moseley's original papers should be consulted.

THE IONISATION CAUSED BY X RAYS.

Within recent times W. H. Bragg suggested that the X rays themselves are unable to ionise a gas (or other substance) through which they pass, the ionisation which is observed being due to the secondary cathode particles produced by the X rays.

The explanation of many X-ray phenomena is much simplified by this view, and the hypothesis has received strong experimental confirmation.

C. T. R. Wilson showed in 1897 that when moist air is ionised in a vessel, and is allowed to expand suddenly within certain definite limits, water condenses on the ions and a fog is formed.

This has been utilised by him in the experiments in question. To quote from his paper (*Proc. Roy. Soc.* Series A, vol. 85, June, 1911):

"When the air is allowed to expand while exposed to the radiation from an X-ray bulb the whole of the region traversed by the primary beam is seen to be filled with minute streaks and patches of cloud, a few due to secondary X rays appearing also outside the primary beam. A photograph shows the cloudlets

to be mainly small thread-like objects not more than a few millimetres in length, and many of them being considerably less than $\frac{1}{10}$ mm. in breadth. Few of them are straight, some of them showing complete loops. Many of them show a peculiar beaded structure. In addition to the thread-like cloudlets, there are minute patches of cloud which may be merely foreshortened threads. Other fainter and more diffuse patches and streaks are also present, possibly representing older trails, in which the ions have had time to diffuse considerably before the expansion.

"The droplets composing the threads have been deposited on the ions produced along the paths of the actually effective ionising rays. These are probably of the nature of easily absorbed

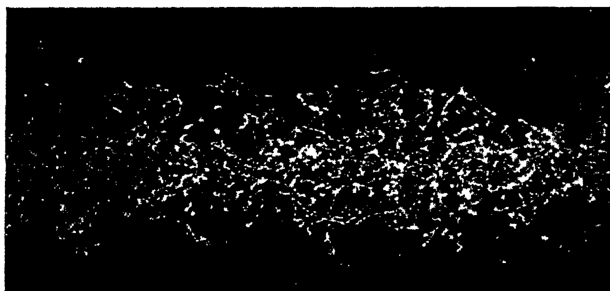


FIG. 7.

secondary beta- or cathode-rays; some doubtless starting from the roof or floor of the cloud chamber, others, however (the larger number when a limited horizontal beam of X rays is used), originating in the gas. The results are in agreement with Bragg's view that the whole of the ionisation by X rays may be regarded as being due to beta- or cathode-rays arising from the X rays."

Fig. 7 illustrates the ionisation in the track of a beam of X rays; the thread-like objects are ions upon which water vapour has condensed, thus making them visible. It will be seen that the ionisation appears to be due to some kind of very easily deflected radiation, *e.g.* cathode rays.

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CHAPTER V

RADIO-ACTIVE SUBSTANCES

THE discovery of radio-active substances followed close upon that of the X rays. Henri Becquerel in 1896 was led to examine substances which were known to phosphoresce under the influence of light, with a view to seeing whether they emitted any rays similar to X rays. Uranium salts when exposed to light are phosphorescent, the effect lasting for some time after the exposure. Becquerel found that uranium salts when first exposed to sunlight, and then laid upon a photographic plate wrapped in black paper, gave an impression upon the plate after development. He subsequently showed, however, that the initial exposure to sunlight was not necessary, for uranium salts which had been prepared in the dark were just as effective photographically; in fact, the phosphorescence associated with the body had nothing to do with the phenomenon. Moreover, Becquerel found that the power of affecting a photographic plate was shown by uranium itself as well as by its salts, and was therefore attributable to the element uranium.

These photographic effects could not be ascribed to any vapour emitted by uranium, for similar effects were obtained by interposing a thin sheet of glass between the substance and the photographic plate. The effect was not found to diminish in intensity with time, which indicated that the uranium was continuously emitting some form of radiation.

This discovery of Becquerel was the first substantiated case of a body spontaneously emitting rays, and the name "radioactive" was given to bodies possessing such a property.

It was also shown by Becquerel that the rays from uranium were able to discharge electrified bodies; in other words, they

ionised the air through which they pass, as X rays do, and certain substances fluoresced under their action. The three distinguishing features of X rays, their photographic, ionising and fluorescent action are therefore seen to be exhibited by a body like uranium *spontaneously*.

During an investigation of the relative radio-activities of minerals containing uranium, Madame Curie made the discovery that some of them were even more active than uranium itself. For example, pitchblende from Joachimstal contains from 50–80 per cent. uranium, and its activity was found to be from 3–4 times greater than uranium. This indicated the presence of some other radio-active body or bodies in the mineral. As the result of a systematic attempt to isolate other radio-active bodies from pitchblende, Prof. and Mdme. Curie in 1898 effected the separation of two such bodies, radium and polonium, which were intensely radio-active when compared with uranium.

Pitchblende subsequently yielded another radio-active body, actinium, which was isolated by Debierne and independently by Giesel, who gave it the name emanium, after his discovery that it emitted a radio-active gas similar to an emanation. When the identity of emanium and actinium was proved, it was agreed to keep the name actinium for this substance.

THE CRITERION OF RADIO-ACTIVITY.

Before proceeding further, it may be as well to distinguish clearly between radio-active substances and many agents which simulate their effects.

The parallelism just indicated between the properties of X rays and those of the radiation from uranium apparently renders such a distinction a matter of difficulty, but this is only because attention is directed to the effects of the rays without considering their source. The production of X rays from a bulb is at the discretion of the operator, whereas the radiation from uranium is essentially spontaneous ; it is not subject to our control, and is independent of any chemical combination that the uranium may participate in. Apart from its spontaneity, however, there

is another property of radio-active substances which serves to classify them as such.

Associated with the radiation from a radio-active body there is always a transformation of one kind of atom into another. The dream of the alchemist has been anticipated by Nature; but whereas the alchemist hoped to transmute bodies of low atomic weight into those of higher (*e.g.* lead to gold), the process as exhibited in Nature is always in the opposite sense, namely, the breaking down of elements into others of lower atomic weight.

When these two distinguishing features of radio-active substances are borne in mind there is little likelihood of confusing them with other bodies or agents which, under specified conditions, may simulate some of their effects.

It was not long after Becquerel's important discovery that other radio-active substances were brought to light. Madame Curie and Schmidt independently discovered that thorium compounds possessed similar properties to those of uranium in continuously emitting rays.

THE SEPARATION OF RADIO-ACTIVE BODIES.

The separation of radium and polonium from pitchblende is an exceedingly laborious process, the main principles of which may be found in *Comptes Rendus*, 1898, p. 1215, and "Radio-active Substances," *Chemical News*, 1903, Mdme. Curie.

Radium is chemically allied to barium, and the process essentially consists in effecting certain chemical separations, at each stage of which the radio-activity of the two parts is tested. The more active specimen is still further treated until, by repeated chemical fractionations, a sample of the chloride or bromide of radium mixed with that of barium is obtained which is enormously more active than uranium.

The final separation may be effected by fractional crystallisation, radium chloride being less soluble than barium chloride. Giesel has shown that the bromide is more easily separated than the chloride, and specimens of practically pure radium bromide were first prepared by him.

By similar chemical processes to the above, two other substances, polonium and actinium, were isolated from pitchblende.

It is seen that the separation of these radio-active bodies has been along strictly chemical lines, their recognition, however, being almost entirely dependent upon electrical measurements of the effects they give rise to.

To give some idea of the labour involved in the separation of radium from Austrian pitchblende, it may be stated that from one ton of this substance about half a gram of radium is obtained. No natural deposit yet found exceeds the Austrian pitchblende in its radium content.

THE CHEMICAL PROPERTIES OF RADIUM, POLONIUM AND ACTINIUM.

Radium is chemically allied to barium. It forms a chloride and sulphate, which latter is very insoluble. The crystalline bromide $RaBr_2 2H_2O$ is quite soluble, especially in a weak solution of hydrochloric acid. The atomic weight of radium has been determined independently by Madame Curie and by Thorpe, and found to be 226.5. It gives a characteristic spectrum analogous in some respects to the spectra of elements to which it is chemically allied. Polonium is closely allied chemically to bismuth and actinium to thorium.

Neither polonium nor actinium has been isolated in quantities sufficiently large to allow of any determination of their atomic weights, nor indeed to give any characteristic spectral lines.

The chemical actions which the rays from radio-active bodies may give rise to will be considered in Section II.

THE RELATIVE ACTIVITIES OF THE DIFFERENT RADIO-ACTIVE SUBSTANCES.

The radio-active bodies which have so far been considered are uranium, thorium, radium, polonium and actinium. The number of radio-active bodies known at the present time is about thirty; but it may be useful at the present stage to give some idea of the relative activities of these five bodies, for they stand at the beginning or at the end of a series of changes which are best considered separately.

Uranium and thorium are weight for weight of about the same activity. By the activity of a radio-active body is meant the

extent to which it is capable of exhibiting the three most marked characteristics of radio-active bodies, namely, photographic, fluorescent and ionising action. Radium has been estimated to be about two million times as active as uranium, polonium is several thousand times as active as an equal quantity of radium, and Boltwood has shown that the activity of actinium, as occurring in Nature, is of the same order as uranium and thorium; but, if pure, it has been estimated that it would have about the activity of radium.

These statements must be followed by another to the effect that, generally speaking, the more active a substance is, the less there is of it. It will subsequently appear that bodies are known which have several thousand times the activity of polonium. Here again the consideration holds—the amounts of such substances available are minute; far beyond the limits of detection of the most delicate balance. If the electrical method of detecting these substances had not been adopted, it is safe to say that practically nothing would be known about radio-activity.

METHODS OF MEASUREMENT OF RADIO-ACTIVE SUBSTANCES.

The ionising action of the rays emitted by radio-active bodies serves as the most convenient and accurate basis for the measurement of their activities. Their photographic and fluorescent action may, however, be made use of in certain cases, especially when the result aimed at is not quantitative but qualitative, though under some conditions these methods may be applied with precision.

The electrical measurements of the ionising action are usually carried out by means of a gold-leaf electroscope or a quadrant electrometer. A modern type of quadrant electrometer is the Dolezalek instrument, for details of which the original memoir may be consulted (*Instrumentenkunde*, p. 345, 1901). Although much simplified in construction, this electrometer with its necessary attachments is still a somewhat complicated measuring instrument, and is not so commonly used as the electroscope.

The method of using a gold-leaf electroscope has already been detailed in a previous section, and the various types in use will be considered in Chapter XI.

The rays from the radio-active substances are complex, and are known as the alpha, beta and gamma rays, and the particular form of measuring instrument to be used has to be selected to suit the type of radiation whose measurement is required.

THE URANIUM, RADIUM, THORIUM AND ACTINIUM SERIES.

It has been found that radium is an intensely active substance compared with uranium. It has a "Time Period" (*vide* p. 44) of about 1690 years, and unless its supply were continually replenished from some store, then, to account for the quantities which are found in the earth at the present time, it has been deduced by Rutherford that 26,000 years ago the earth would have had to consist practically entirely of radium. Rutherford and Soddy suggested that some substance present in pitchblende is actually producing radium.

By examining a large number of minerals containing uranium, Boltwood showed that with few exceptions the ratio of the amount of radium to the amount of uranium present was practically constant. The constant association of these two substances has led to the view, now generally accepted, that radium is in the direct line of radio-active descent from uranium. There are, however, intermediate substances, the scheme being conveniently represented in Table 11.

TABLE 11.—THE URANIUM SERIES.

Substance.	Time to decay to half value.	Radiation emitted.
Uranium (1 and 2)	5×10^9 years	Alpha
Uranium X	24.6 days	Beta and gamma
Ionium	3.5×10^5 years	Alpha
Radium	1690 years	Alpha, beta and gamma (beta and gamma very weak).

Uranium probably consists of two bodies—Uranium 1 and Uranium 2—but they are not separable. Uranium Y is a lateral product of one of these bodies, and is not included in the table of direct descent.

The above scheme represents what is believed to take place atomically in the radio-active bodies. The expulsion of an

alpha particle from an atom of uranium converts it into UrX, a much more unstable atom, which emits beta and gamma rays, and is converted into ionium where the return to a more stable condition is indicated by the longer time period. It must, however, be understood that the time periods have no reference to the individual atoms, but only to collections of a very large number of them.

The radium series. Although radium does not stand in quite the same category as uranium and thorium as being the first member of a radio-active series, *i.e.* as having no known forerunner, it is convenient to consider it as the head of the series to which it gives its name. Of late years there have been several indications that substances previously thought to be single substances are in reality complex, this notably in the case of RaC_1. The recent work of Fajans, among others, goes to show what may almost be termed an uncertainty in the radio-active process. It seems that some of the atoms of RaC_1 are converted into radium D, and others into RaC_2, but what it is that decides the alternative is still a matter of conjecture.

TABLE 12.—THE RADIUM SERIES.

Substance.	Time to decay to half value	Radiation emitted.
Radium - - -	1690 years	Alpha and weak beta
Ra. Emanation - -	3.85 days	Alpha
Radium A - - -	3.0 minutes	Alpha
Radium B - - -	26.8 minutes	Beta and gamma
Radium C (complex, probably consisting of 3 bodies) - -	19.5 minutes	Alpha, beta and gamma
Radium D - - -	16.5 years	Beta
Radium E - - -	5.0 days	Beta and gamma (gamma very feeble)
Radium F (Polonium) ↓ (Probably Lead)	136 days	Alpha

In the earliest schemes representing radio-active series some substances appeared as ray-less products, and others giving out

a complex type of radiation. These cases have been the subject of considerable attention, notably by Hahn and Meitner.

The general radio-active characteristics of the substances comprised in the radium series will be seen from Table 12. The names of the substances are arranged in genealogical order, the second and third columns giving the Time Period of each substance and the radiation it emits.

The final radio-active product of the series RaF is identical with the substance isolated by Mdme. Curie, which she named polonium. It has a period of 136 days, and there are grounds for believing that on emitting alpha particles it is converted into lead; but of this there is not as yet any conclusive experimental evidence.

The actinium series. The genealogy of actinium is at present obscure. Suggestive evidence has been brought forward that it is a lateral product of one of the members of the radium series. It has not yet been isolated nor prepared in sufficient quantities to give a molecular weight determination or spectroscopic evidence of its existence. Yet it gives rise to a typical radio-active series, including a gaseous product, which by analogy is known as actinium emanation. The data referring to the successive members of this series will be found in Table 13.

TABLE 13.—THE ACTINIUM SERIES.

Substance.	Time to decay to half value.	Radiation emitted.
Actinium	30 years	Beta
↓		
Radio-actinium -	19.5 days	Alpha
↓		
Actinium X	11.4 days	Alpha
Act. Emanation -	3.9 seconds	Alpha
Actinium A -	.002 second	Alpha
Actinium B -	36 minutes	Beta and gamma
Actinium C -	2.1 minutes	Alpha
Actinium D -	4.71 minutes	Beta and gamma
↓		
?		

The thorium series. Thorium is the first member of a long series of radio-active substances, many of which were discovered by Hahn. Data for successive members of the series may be found in Table 14.

TABLE 14.—THE THORIUM SERIES.

Substance.	Time to decay to half value.	Radiation emitted
Thorium - - -	1.3×10^{10} years	Alpha
↓ Meso-thorium 1 - -	6.7 years	Beta
↓ Meso-thorium 2 - -	6.2 hours	Beta and gamma
↓ Radio-thorium - -	2.0 years	Alpha
↓ Thorium X - - -	3.65 days	Alpha
↓ Thorium Emanation -	54 seconds	Alpha
↓ Thorium A - - -	.14 second	Alpha
↓ Thorium B - - -	10.6 hours	Beta
↓ Thorium C (complex, probably three bodies)	1 hour	Alpha, beta and gamma
↓ Thorium D - - -	3.1 minutes	Beta and gamma
↓ ? Bismuth		

This series again shows the extraordinary variations met with in radio-active phenomena. Starting with one of the most stable radio-active bodies, thorium, there follow four bodies of alternating length of period before the formation of a gaseous product, the emanation, having the very short time-period of 53 secs.; the four remaining bodies, ThA, ThB, ThC and ThD, have comparatively short lives and are of a solid nature.

At one time it was considered unlikely that any substance would be separated from this series approaching in activity and quantity that of radium, but Hahn has been able to separate out from thorium highly concentrated preparations.

The active substances separated are three, namely, meso-

thorium I., meso-thorium II., and radio-thorium, with time-periods of 5.5 years, 6 hours, and 2 years respectively. No radiation has so far been detected from the first member, the second emits beta and gamma rays, while radio-thorium emits only alpha rays. As the constituents have rather short time-periods compared with radium, these preparations will not have the same permanency as radium. The diminution in the beta and gamma ray intensity of an originally pure meso-thorium preparation does not, however, begin for ten years, owing to an intermediate increase in the activity. At the end of the next ten years the activity will be reduced to 50 per cent. of that of the original preparation.

The curve in Fig. 8 shows the initial rise in the gamma ray activity of freshly prepared meso-thorium.

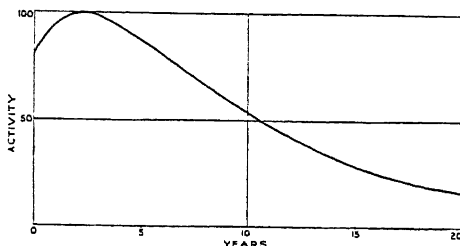


FIG. 8

It is unlikely that the thorium emanation will have much clinical application when separated from its parent substance thorium X, owing to its extremely short time-period (54 secs.). Continuous bubbling of a stream of air through a thorium solution could, however, be made to provide the emanation as quickly as it decays.

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CHAPTER VI

THE RADIATIONS FROM RADIO-ACTIVE BODIES

THE radiation emitted by radio-active bodies is complex. It consists as stated of three types, which are known as alpha. beta and gamma rays. These rays exhibit striking differences from one another, as the following considerations will show.

The alpha rays. These have been shown by Rutherford to consist of positively charged helium atoms ejected from radio-active bodies with high velocity. The velocity of the alpha particles depends upon the body from which they are expelled, but from any one particular substance they are all ejected with the same velocity. The average velocity of these particles from various radio-active bodies is about $\frac{1}{10}$th of the velocity of light.

The conception of radiation is in modern times confined to that of an ether vibration of some kind, but before the real nature of the alpha particle was known it was recognised that something resembling a radiation was proceeding from the bodies emitting these particles. These high velocity atomic particles are consequently usually referred to, though really incorrectly, as alpha "rays"; the term "alpha particles" is also in use.

The beta rays. The observation was made almost simultaneously by Giesel and by Meyer and Schweidler that these "rays" consist of negatively charged particles. Measurements were made showing that they were deflected by magnetic fields in the same manner as the particles of the cathode stream, and they were therefore proved to be negatively electrified particles.

Subsequent experiments, entailing the deflection of the rays by an electric field, established the fact that the beta rays are negative electrons travelling with very high velocities. As in the

case of the alpha rays, the velocity depends on the substance from which they are emitted; but the beta rays emitted by a single radio-active body may have very different velocities.

It will be remembered that the particles in the cathode stream have an average velocity of about $\frac{1}{10}$th of the velocity of light, but the beta particles from radio-active substances are characterised by a rather higher velocity, for velocities have been measured ranging from .2V to .98V, V being the velocity of light.

The gamma rays. These rays were discovered by Villard, and all observations so far made upon them indicate that they are analogous to X rays, and consist of vibrations of the ether. They are not deviated by the most intense magnetic and electric fields, and are characterised by an extraordinary penetrating power through substances opaque to light. No attempt has been made to measure the velocity of the gamma rays; their close resemblance to X rays indicates the probability of their having a velocity equal to that of light.

Before proceeding to a more detailed consideration of the various properties of these three types of rays, it is of interest to note that they each have their counterpart in an X-ray bulb.

The canal rays consisting, under certain conditions, of positively charged helium atoms are low-velocity alpha particles.

The particles of the cathode stream are low-speed electrons, *i.e.* slow beta particles.

The X rays are, as far as is known, identical with gamma rays of comparatively small penetrating power.

It will be noticed that in each case there is a diminished velocity or penetrating power where these agents have been provoked artificially. Despite the resources at our disposal their application lacks the effectiveness of the natural mechanism of radio-active processes.

PROPERTIES OF THE RADIATIONS.

1. **Alpha rays.** These rays affect a photographic plate, cause many bodies to fluoresce brilliantly, and have very intense ionising power.

The photographic action of the alpha particles frequently provides a convenient means of their detection, but does not lend itself to quantitative measurement, unless certain special precautions adopted by Kinoshita in the preparation of the film are complied with.

The fluorescence caused in many substances by alpha rays is beautifully exhibited in the spinthariscope of Crookes. A speck of radium is placed near a screen of zinc sulphide which, when viewed in the dark with a magnifying lens, is seen to scintillate, each alpha particle as it strikes the screen producing a flash which almost instantaneously fades.

This action has been studied by Rutherford and Geiger and by Regener, who have shown that it provides a means of counting the number of alpha particles emitted per second by radio-active bodies; for, under suitable conditions, each alpha particle produces a single scintillation.

The ionising action of the alpha particles is very intense. This offers the most convenient method of comparing the relative activities of different sources of these rays; but great care must be taken that the layers of material to be compared are of exactly the same thickness, otherwise absorption of the rays by the material itself may render the measurements valueless. The rate of discharge of an electroscope being proportional to the ionisation of the air within it, which in turn is proportional to the activity of the exciting agent, this provides a simple method of measurement. The ionisation by these rays being very intense, it is essential for accurate observations that "saturation" (see p. 10) should be obtained.

The penetrating power of the alpha particles is quite small. Despite their high velocity, they are very easily stopped by obstacles placed in their path. In their passage through air they are stopped by their numerous impacts with the gaseous molecules which they meet in the course of their flight.

The distance they go depends upon their initial velocity. The greatest distance in air, the "range," as it is called, that these particles travel, varies for different radio-active bodies. The greatest range is 8.6 cms., which is that of the alpha particles from thorium C_2. The penetrating power of alpha particles through substances such as water or aluminium is very small, and, although not accurately so, the range in many substances

may be taken to be approximately inversely as the density of the material through which the alpha particle is passing. For instance, if the range of an alpha particle in air is 5 cms., in aluminium it will be $\frac{5}{2000}$ = .0025 cm., aluminium being just about 2000 times as dense as air.

By a comparison between the ionisation caused by alpha particles and their absorption in different gases, it has been shown that the greater the absorption the more intense is the ionisation. Although this relation has not been substantiated for solids and liquids, it is not improbable that there is a similar association, in which case, although their action is restricted to a very small depth of tissue, a local effect of considerable intensity may result. These rays are very easily absorbed by interposing a thin screen of aluminium or mica less than .1 mm. thick.

When alpha rays come into contact with matter, they liberate low-velocity electrons, which constitute a type of easily absorbed secondary rays. These electrons are even more readily absorbed than the alpha rays themselves. Recently Chadwick has shown that gamma rays may also originate when alpha rays are stopped.

2. **Beta rays.** Compared with the alpha rays these rays are generally not so striking in their effects. They are less active photographically, their fluorescent action on most substances is less brilliant, and their ionising power is feebler. If electroscopic measurements be made of a substance giving out alpha and beta particles in equal numbers, the ionisation due to the beta particles is usually about 1 or 2 per cent. of that caused by the alpha particles.

The beta rays are capable of penetrating a considerable thickness of solid or liquid before being completely absorbed. The penetrating power depends upon both the velocity of the rays, which has been seen to extend between fairly wide limits (p. 49), and the density of the substance through which they are passing.

The terms "hard" and "soft" are sometimes applied to these rays to distinguish between easily absorbed radiation and that of a penetrating type; 1 mm. of aluminium cuts off the majority of "soft" beta rays.

The study of the absorption by matter of the beta rays presents many difficulties. On introducing an absorbing screen into the path of a beam of beta rays, it has been shown that a partial reflection or scattering of the beam takes place as well as a true

absorption by the matter, added to which another type of radiation, viz. gamma rays, is set up when the beta rays are stopped.

Several of the members of the radium series (p. 44) emit beta rays which vary considerably in velocity, and hence in their penetrating power. For purposes of illustration we will select the beta rays from the radio-active body, radium E, which are on the average a little more penetrating than those of radium B, but less so than those of radium C.

The data in Table 15 show the gradual reduction in the ionisation when increasing thicknesses of aluminium are placed in the path of the rays.

TABLE 15.

Mms. of Aluminium	Ionisation.
0	100
.1	65
.2	42
.4	17.3
.6	7.0
.8	3.2
1.0	1.3

It is thus seen that 1 mm. of aluminium reduces the ionisation to about 1 per cent. of its initial value. For purposes of comparison of the penetrating power of beta (or gamma) rays from different substances, it is inconvenient to have to refer to a whole series of data, and it is more usual to refer to the "coefficient of absorption" of some material (usually aluminium in the case of beta rays and lead in the case of gamma rays), which at once specifies the order of penetration of the rays.

It will be remembered that the criterion for the homogeneity of a beam of X rays is that on interposing equal thicknesses of absorbing screens in the path of the beam, the ionisation on the far side of the screens should diminish according to a simple exponential law; the test for which is that when the logarithms of the numerical values of this ionisation are plotted against the thickness of matter traversed, the points shall lie on a straight line. Now, in the case of beta rays from a radio-active body, while many observations go to show that this same law of absorption holds,

this does not mean that the beta rays from one and the same body all have the same velocity. In fact, Gray and Wilson have shown that a beam of beta rays which is absorbed by aluminium according to an exponential law may be heterogeneous.

Applying this test to the experimental values of Table 15, the logarithms will be found to lie on a straight line. Selecting any two points on this line, the *difference* of the logarithms corresponding thereto multiplied by 2.302 and divided by the thickness in cms. of material interposed gives the coefficient of absorption $\lambda = 43.3$ of the absorbing substance for the beta rays in question.

A comparison of these coefficients shows at once the relative penetrating power of the rays, as may be seen from Table 16.

TABLE 16.

ABSORPTION COEFFICIENTS OF BETA RAYS IN CM^{-1} OF ALUMINIUM.

Radium B.	Radium C.	Radium E.
13–91	13	43·3

Fajans and Makower have shown that the ionisation produced by the hard beta rays from RaB($\lambda = 13$ cm.$^{-1}$) amounts to only about 1½ per cent. of the whole ionisation caused by the beta rays from this body; hence most of the beta rays from RaB are an easily absorbed type.

The more penetrating the rays the smaller the coefficient. It will be noticed that the beta rays from radium C are nearly six times as penetrating as those of radium B. From the previous table it was seen that 1 mm. of aluminium reduced the beta rays from radium E to about 1 per cent. of their initial value. To obtain a similar reduction for these rays from RaC $\frac{43.3}{13.5}$, *i.e.* about 3.2 mm. would be required. The beta rays issuing from this thickness would, however, be high-velocity rays, the slow and medium rays also present in the original heterogeneous beam having suffered complete absorption.

More recent observations upon the beta rays from radium have shown that they are even more heterogeneous than had previously been thought.

Danysz was able to isolate 23 distinct beams of homogeneous

beta rays from RaB and RaC, *i.e.* bundles of rays having appreciably different velocities.

More recently Rutherford and Robinson have examined the beta radiation from these two bodies, and have isolated altogether 64 beams of beta rays which are emitted by these two bodies, 16 of which came from RaB, having velocities ranging from .365V to .823V, and 48 from RaC, having velocities ranging from .632V to .9858V, where V is the velocity of light.

The data hitherto presented are not such as to give a ready answer to the enquiry as to how far the beta rays penetrate the tissues of the body. This is a frequent consideration in radium-therapy when the relatively large ionising power of the beta rays compared with the gamma rays is borne in mind.

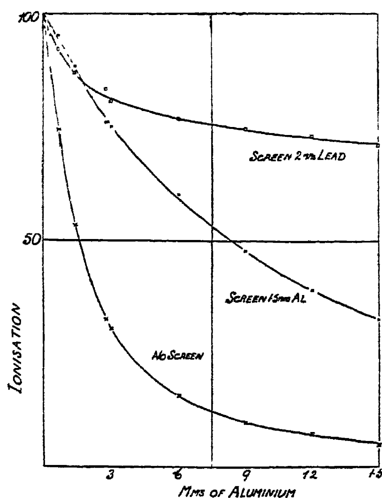


Fig. 9.

With a view to being able to answer this question, the following experiments were made by Russ upon the penetration of the composite beta rays emitted by a flat applicator containing radium emanation; the face of the applicator was screened by a thin sheet of mica about .05 mm. thick to stop the alpha rays, and the absorption of the beta rays emitted measured under various conditions.

The composite radiation from the unscreened applicator is very rapidly absorbed by aluminium sheets placed in front of it; this may be seen from the lowest curve (Fig. 9), the ionisation being reduced to about one-tenth of its initial value in going through .9 mm. of aluminium. If the rays from the applicator are first screened by 1.5 mm. of aluminium, the same Fig. shows that the thickness .9 mm. now only reduces the ionisation to 47.5 per cent. of its initial value. The applicator was then screened with 2 mm. of lead, and a similar series of measurements made. The data of special interest here are those at the beginning of the top curve of the same diagram. They show that there is a

soft component present (almost certainly secondary gamma rays produced in the lead), which actually makes the curve dip below the preceding one, although the bulk of the radiation, as the rest of the curve shows, is much more penetrating.

The heterogeneous nature of the composite radiation having been studied in aluminium, the extent to which the more easily absorbed of these rays (curves 1 and 2) penetrate various tissues has been found. The tissues were those of the sheep; they were mounted on wooden blocks, frozen, and thin layers (0.65 mm. thick) cut with a large-size microtome, and then mounted on a thin mica frame in front of the window of the ionisation vessel. The absorption by the tissues of the unscreened rays from the applicator was first measured, and then when the rays were screened by 1.5 mm. of aluminium, the data for which are collected in Table 17.

TABLE 17.—ABSORPTION OF COMPOSITE RAYS FROM FLAT APPLICATOR.

No Screen.

Thickness of Tissue.	Nature of Tissue.				
	Muscle (density 1.25). Ionisation.	Liver (density 1.21). Ionisation.	Spleen (density 1.17). Ionisation.	Brain (density 1.12). Ionisation	Fat (density 0.92). Ionisation.
0 mm.	100	100	100	100	100
0.65 "	32.5	36.0	36.7	36.8	40.2
1.30 "	—	18.0	—	—	—
1.95 "	10.3	11.4	12.4	12.2	13.0
3.25 "	4.5	5.4	5.8	5.7	6.4
4.55 "	2.3	3.5	3.1	3.5	3.4

Screen 1.5 *mm. Aluminium.*

Thickness of Tissue.	Muscle. Ionisation.	Spleen. Ionisation.	Brain. Ionisation.
0 mm.	100	100	100
0.65 "	85.5	90.0	—
1.95 "	62.0	56.2	57.0
3.25 "	43.0	41.4	36.6
4.55 "	26.3	29.9	26.7

Absorption measurements are more easily and accurately made with a substance like aluminium than with tissues. When the coefficient of absorption (λ) of beta rays has been found in aluminium, the above measurements indicate that no very serious errors would generally be introduced if the coefficient of absorption of these same rays in a tissue were reckoned from the simple relation—

$$\text{Coefficient of absorption in tissue} = \text{coefficient in aluminium} \times \frac{\text{density of tissue}}{\text{density of aluminium.}}$$

In blood-containing organs such as spleen, liver, etc., however, this process would probably give rather higher values than the actual absorption coefficients.

When a flat applicator is applied to the skin under clinical conditions, the radiation through succeeding layers becomes weaker both on account of the absorption the rays suffer and their spreading out from the source.

3. **Gamma rays.** These rays are not so active photographically as the alpha or beta rays, and their fluorescent and ionising powers are also not so intense. If ordinary electroscopic measurement be made of a substance emitting beta and gamma rays, the ionisation due to the gamma rays will generally be found to be only a few per cent. of that due to the beta rays. This proportion, however, varies, for whereas in the case of a member of the radium series the gamma rays account for 2 per cent. of the combined beta and gamma ray ionisation, this percentage is nearly 100 times less in the case of a member of the uranium series. This distinction is an important one, and it is probable that the further study of such differences will reveal some connection between the beta and gamma rays emitted by radio-active bodies.

Bearing in mind the small ionisation of the beta rays compared with that of the alpha rays, it will be gathered that the gamma rays are much less effective than the alpha rays in producing ionisation.

There is some difficulty in such a comparison, for whereas it is quite justifiable to speak of the number of alpha and beta particles emitted per second from radio-active bodies, these numbers having in fact been measured in some cases, no enumeration of gamma rays is possible.

The penetrating power of the gamma rays is much greater than that of the alpha or beta rays.

They correspond on the average to a *very hard* type of X rays, more penetrating, in fact, than any X rays yet produced by mechanical means. The gamma rays from different radio-active substances have different penetrating powers; in fact, from the same substance the gamma rays may be heterogeneous. This has been proved to be the case for the gamma rays from radium (the majority of the gamma rays are not given out by radium itself, but by two members of its series, radium B and radium C).

The terms hard, medium and soft are frequently applied to these rays to indicate their degrees of penetrating power. Generally speaking the absorption of gamma rays is proportional to the density of the substance traversed, but lead absorbs rather more of the rays than its density would indicate, and is therefore very suitable as a screen for these rays. This statement must, however, be qualified by the reminder that when lead is used for this purpose therapeutically, soft secondary rays are emitted by the lead, which necessitate twenty or thirty layers of ordinary lint to absorb them completely.

TABLE 18.

ABSORPTION BY LEAD OF GAMMA RAYS FROM RADIUM C.

Thickness of lead in cms.	Ionisation.	Thickness of lead in cms.	Ionisation.
·3	100	10	.63
1	61.6	11	·39
2	33·1	12	·30
3	19.9	13	.20
4	11.7	14	.11
5	7·07	15	.07
6	4.26	16	.05
7	2.57	17	.04
8	1.62	18	.03
9	1.0	19	.02

The absorption by lead of some of the most penetrating gamma rays, viz. those from radium C, was determined by Tuomikoski, by

measuring in an electroscope, the ionisation caused by the gamma rays after they had traversed 3 mm. of lead. Layers of lead were then interposed in the path of the rays, and the subsequent reduction in the ionisation noted. The data are seen in Table 18.

The wave-lengths of the rays. By methods analogous to those initiated by Laue in his investigations upon the wave-lengths of X rays, Rutherford and Andrade have measured the wave-lengths of the more penetrating gamma rays emitted by radium B and radium C. Previous observations had shown that this radiation was heterogeneous, and this is clearly exhibited in the accompanying table, in which it is shown that the rays which we speak of as a whole as being very penetrating, consist of rays varying very considerably in their wave-lengths.

TABLE 19.—PENETRATING GAMMA RAYS FROM RADIUM B AND RADIUM C.

Transmission Method.		Reflexion Method.	Wave-length Mean.
Absorption.	Reflexion.		
42′	43′	44′	.71 × 10^{-9} cms.
1° 0′	1° 0′	1° 0′	.99
1° 10′	1° 10′	1° 11′	1.15
1° 24′	1° 25′	1° 24′	1.37
{1° 37′	1° 36′	1° 37′	1.59
{1° 44′	1° 44′	1° 44′	1.69
—	2° 0′	2° 0′	1.96
2° 20′	2° 20′	—	2.29
—	—	2° 28′	2.42
—	—	2° 40′	2.62
—	3° 0′	3° 0′	2.96
3° 18′ *	—	3° 18′ *	3.24
—	—	4° 0′ *	3.93
—	—	4° 22′	4.28

SECONDARY BETA AND GAMMA RAYS.

In a previous section attention has been directed to the production of secondary rays when a primary beam of X rays is

* Possibly second order spectrum.

incident upon some obstacle, such as a screen placed in its path. It will be remembered that not only are secondary X rays formed, but also cathode rays. From the analogy between cathode rays and beta rays, and also between X rays and gamma rays, it was to be anticipated that when beta rays were stopped, gamma rays would be generated and that when gamma rays met an obstacle, beta rays would come into existence.

Eve was the first to show that beta rays are set up when gamma rays are incident upon a screen interposed in their path. The intensity of such beta radiation increases with the intensity of the primary beam of gamma rays and also as the density of the matter interposed increases. Generally speaking, the beta rays produced by gamma rays have a very high velocity.

Gray showed the converse effect, namely, when beta rays are stopped there are gamma rays produced, the amount of which increases with the atomic weight of the material used to stop the beta rays. The process is apparently a reversible one; that is to say, starting with a beam of beta rays, we may produce secondary gamma rays, which are in turn capable of producing beta rays as a secondary radiation.

The secondary radiation excited in tissues, when traversed by a beam of gamma rays, has been the subject of measurement by Coutard, who expresses the intensity of this secondary radiation in terms of the intensity of the incident beam of rays. The following are his results:

TABLE 20.

SECONDARY GAMMA RAYS.

Substance.	Percentage of Intensity of the Primary Beam.
Water - - -	3 per cent.
Serum - - -	3·5 ,,
Blood - - -	5 ,,
Tissues - -	7 ,,

The penetrating power of these secondary rays is stated to be less than that of the primary beam of gamma rays. It probably consisted partly of gamma and partly of beta rays.

The secondary rays excited in the tissues when a primary beam of gamma rays passes through them will vary with the nature of the tissues. It is known that substances such as, *e.g.* calcium and iron, when subjected to a suitable beam of X rays, give off secondary X rays which are very soft in type. Hence the irradiation by gamma rays of parts of the body containing these elements must frequently be attended by such secondary rays, which, owing to their easy absorbability, may have considerable therapeutic value.

The clinical importance of secondary radiations, whether induced by beta, gamma or X rays, is difficult to estimate, and yet it does not seem unlikely that many of the reactions occurring are really due to the secondary radiation in one form or another set up by the incident primary beam. This production of a secondary type of radiation, as a result of the gradual absorption of the primary beam of rays, presents many difficulties in the elucidation of the biological effects associated with different types of radiation.

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CHAPTER VII

THE RELATIVE IONISING AND PENETRATING POWERS OF THE ALPHA, BETA, GAMMA AND X RAYS

From the preceding sections it has been seen that the alpha, beta and gamma rays afford very striking contrasts in their properties. As a rough working rule it may be said that the more penetrating a ray is the less it will ionise per unit length of its path, and *vice versâ*. The easily absorbed alpha and slow beta rays are much more active ionising agents than the quick beta and penetrating gamma rays.

To take a concrete example, if a thin layer of some radium salt be spread over a surface and the ionisation in the air of an electroscope caused by its rays be measured, the relative ionisations caused by the alpha, beta and gamma rays will be found to be approximately 10,000, 100 and 1, whereas the relative penetration of these rays is in the inverse order; the beta rays go about 100 times as far as the alpha rays, and some of the gamma rays about 100 times as far as the beta rays.

This statement is only true under specified conditions, and it would be a mistake to suppose that the *total* ionising effect of the beta rays from radium is 100 times as great as that due to the gamma rays. It is probable that the *total* amount of ionisation produced by an alpha, beta or gamma ray is not very different. The important consideration is that the ionisation due to alpha radiation is locally an intense one; that due to the beta rays less intense and less localised; while the gamma rays have a small ionising action, which may, however, be distributed over a very large space.

When alpha and beta rays are passing through matter their speed is gradually reduced, so that they no longer cause the usual

effects (ionisation, etc.) by which they are recognised, and they are then said to be completely absorbed. This slowing-down process was first shown by Rutherford in the case of alpha particles, and by W. Wilson for the beta rays from radium B and radium C.

When we consider the irradiation of some surface condition by radium prepared in such a way that the alpha, beta and gamma rays may be utilised, it will be remembered that the greatest distance to which the alpha particles could penetrate through the tissues would be $\frac{7.06}{788} = .089$ mm., 788 being about the density of epithelial tissue when that of air is taken as unity. From this it is clear that the alpha particles would barely penetrate the epidermis, and therefore would be of little therapeutical significance under these conditions of irradiation. Hence the particular rays which give the most striking physical signs are under many conditions of clinical practice quite eliminated.

The beta rays from radium are heterogeneous, with a wide range in their penetrating power. Restricting our considerations to the most penetrating type, it will be seen that the decrease in intensity in penetrating epithelial tissue (without taking into consideration the decrease with distance, as this varies according to the distribution of the radium) would proceed as follows:

TABLE 21.

Thickness of Tissue.	Intensity.
0	100
.65 mm.	85.5
1.95 ,,	62.0
3.25 ,,	43.0
4.55 ,,	26.3
1.00 cm.	6.2

The numbers in Table 21 indicate that the intensity of these hard beta rays after penetrating 1 cm. of tissue would, owing to absorption alone, be reduced to about 6 per cent. of their value at the surface.

It is thus seen that for any other than superficial conditions

the alpha and beta irradiation of the part in question could only be efficiently carried out by the introduction of the radio-active material by some such means as is indicated on p. 76, or by the injection of some fluid containing it in solution.

This consideration holds when the other radio-active substances are in question, for it will be seen from the following data that the beta rays from radium are the most penetrating of all beta rays.

TABLE 22 SHOWING ABSORBABILITY OF BETA RAYS BY ALUMINIUM.

Substance.	Velocity of Beta Rays.	Thickness of Aluminium to completely absorb Rays. Calculated *
Uranium X	Continuous from about 5 to about 2.53×10^{10} cms /sec.	from 1 mm.– 66 mm.
Radium	$1.56–1\ 95 \times 10^{10}$ cms /sec	less than .1 mm.
Radio-actinium	about 10^{10} cms /sec	,,
Radium D	$1–1\ 17 \times 10^{10}$ cms /sec	,,
Thorium B	$1\ 89–2\ 16 \times 10^{10}$ cms./sec.	.1 mm.–.2 mm
Radium B	$1\ 08–2.46 \times 10^{10}$,,	.1 mm –.48 mm.
Actinium B	,, ,,	,,
Radium C	$1\ 89–2.94 \times 10^{10}$ cms /sec.	.1 mm –about 5 mm.
Radium E	Continuous over a range of moderate velocities	.1 mm.–.3 mm
Meso-thorium 2	$1\ 11–1.98 \times 10^{10}$ cms /sec	.1 mm
Actinium D	2.32×10^{10} cms /sec	35 mm
Thorium C and D	$87–2.85 \times 10^{10}$ cms /sec.	less than .1 mm.–2 1 mm.

The velocity of light is 3×10^{10} cms./sec.

With regard to the penetration of matter by gamma rays, some comprehensive measurements have been made by Soddy and Russell on a large variety of substances, the main results of which are given in Table 23.

It will be seen from this Table that μ/D (the tabulated values have been multiplied by 100 for convenience) gradually diminishes with the density of the absorbing material and then rises again. If this ratio μ/D were constant it would mean that the extent to which the gamma rays are absorbed is simply proportional to the density of the absorbing screen. That there is the above variation in μ/D shows that this is not quite true.

* Calculated by means of relation given by W. Wilson, *Proc. Roy. Soc.* vol. 82, A. 1909.

TABLE 23.

RELATIVE ABSORPTION OF GAMMA RAYS FROM RaC BY VARIOUS SUBSTANCES.

Material.	Density D.	Coefficient of Absorption μ	100 times $\frac{\mu}{D}$	Thickness required to reduce the intensity to $\frac{1}{2}$. (Calculated.)
Mercury - -	13.59	.642	4.72	1.08 cms.
Lead - - -	11.40	.495	4.34	1.40
Copper - -	8.81	.351	3.98	1.97
Brass - -	8.35	.325	3.89	2.06
Iron - - -	7.62	.304	3.99	2.28
Tin - - -	7.245	.281	3.88	2.46
Zinc - - -	7.07	.228	3.93	3.03
Slate - - -	2.854	.118	4.14	5.86
Aluminium -	2.77	.111	4.06	6.24
Glass - -	2.52	.105	4.16	6.60
Sulphur - -	1.785	.0782	4.38	8.86
Paraffin wax -	.862	.042	4.64	16.50

The last column gives the calculated thickness of any of these substances which would be required to reduce the intensity of a beam of penetrating gamma rays from radium C to one-half of its value.

If aluminium be selected for comparison purposes, reference to the various data given shows that for the soft beta rays to be reduced to half intensity a thickness of .015 cm. is necessary, for the medium beta rays .085 cm., and for the hardest beta rays .2 cm., in comparison with 6.24 cms., the thickness required for the hard gamma rays of radium.

When the gamma rays from other radio-active bodies are examined it is found that thorium D emits gamma rays which are slightly more penetrating than those from radium C, whereas those from meso-thorium 2 and uranium X are less so. This may be seen from the data in Table 24.

The gamma rays from thorium D are about 8 per cent. more penetrating through lead than the gamma rays from radium C. In the case of meso-thorium 2 and uranium X they are about 20 per cent. and 30 per cent. respectively less penetrating.

When a substance like glass is in question they are only 7 and 14 per cent. less penetrating.

TABLE 24.—PENETRATING POWERS OF THE GAMMA RAYS FROM DIFFERENT RADIO-ACTIVE BODIES, THOSE FROM RADIUM C BEING TAKEN AS UNITY.

Absorbing substance.	Radium C.	Thorium D.	Meso-thorium 2.	Uranium X
Lead - -	1.00	1.08	.808	.69
Glass - -	1.00	1.18	.93	.862

This is a consideration which should be borne in mind when clinical conditions under radium and meso-thorium are compared.

Rutherford and Richardson have made an analysis of the gamma rays from radium B and radium C. They have shown that the gamma rays from radium C are essentially all of one type, viz. a very penetrating type, having a coefficient of absorption .115 cm.$^{-1}$ in aluminium and .50 cm.$^{-1}$ in lead (compare values of Soddy and Russell .111 and .495). On the other hand, they found that the gamma rays from radium B, discovered by Makower and Moseley, consist of at least two distinct groups of rays with absorption coefficients 40 cm.$^{-1}$ and .51 cm.$^{-1}$ in aluminium.

The absorption of the gamma rays from radium by various organic substances has been measured by Giraud and compared with that of water with the following results :

TABLE 25.

Substance.	Coefficient of absorption μ.	Thickness required to reduce the intensity to one-half.
Water - - -	.034	20.4 cms.
Serum - - -	.038	18.3 ,,
Blood - - - -	.048	14.4 ,,
Muscular tissue - -	.091	7.6 ,,

It is often desirable to have some means of expressing the radiation from an X-ray bulb, working under specified conditions,

in terms of the corresponding radiations from some standard radio-active substance. There are many ways in which attempts have been made to measure X rays. For radio-active bodies there are few methods which can compare with the ionisation method for accurate quantitative comparisons, and this is probably also the case for X-ray measurements.

The rays from an X-ray bulb vary in quantity and character according to the conditions under which the bulb is worked, consequently when a comparison is made between the ionisation produced by an X-ray bulb and that produced by a known quantity of radium, it will probably only refer to one set of working conditions, and that large variations have been found in this quantitative comparison is therefore not surprising. A comparison made by Eve showed that the ionisation from an X-ray bulb working at a spark gap of 30 cms. gave in an electroscope an ionisation equivalent to that produced by the gamma rays from 2.15 grams of radium. Russ found that for a bulb running at 19 cms. spark gap the soft rays from which were cut off by 1.12 mm. of aluminium, the ionisation produced was equivalent to that produced by the gamma rays from 8.88 grams of radium, and that this equivalence rose to 53.8 grams when the spark gap was reduced to 9 cms. and most of the "soft" rays, *i.e.* the highly ionising rays, were utilised.

The equivalence recorded refers to the primary X rays, which are believed to be of the same nature as the gamma rays from radium. It has been seen that the alpha and beta rays are much more effective than the gamma rays in ionising air, and consequently the above equivalence is much reduced when the effects of the X rays are compared with the effects of the alpha and beta rays.

It is, however, difficult in these cases to give data which would be useful for ordinary therapeutical work, for the data would not only be dependent upon the working conditions of the bulb, but also upon many details in connection with the application of the radium.

Generally speaking, the penetrating power of X rays lies between that of beta and gamma rays. It is, however, possible to produce X rays which are more easily absorbed than swift beta rays; and, on the other hand, "very hard" X rays are more penetrating than the softer types of gamma rays. For

purposes of comparison, it may be stated that "very soft" X rays are about as penetrating as "hard" beta rays. The question as to how nearly the X rays approach in penetrating power that of the hard gamma rays of radium cannot be answered without specifying the substance which is used to test the penetrating power. For example, if a comparison be made in this respect for lead, it is found that the "very hard" X rays emitted from the Coolidge tube under a spark gap of 30 cms. (points), and screened by nearly 2 mm. of lead and 7 mm. of aluminium, have about one-thirtieth of the penetrating power of hard gamma rays; if, however, the comparison be made with aluminium under the same conditions, the X rays have a penetrating power of nearly one-fifth of that of the gamma rays, and nearly one-fourth if the comparison be made with water (tissues). Expressed otherwise it may be said that very "hard" X rays have about twice the wave-length of the "hardest" gamma rays of radium.

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CHAPTER VIII

THE DISINTEGRATION THEORY OF RADIO-ACTIVITY

HAVING dealt with the occurrence in nature of several radio-active bodies and with the different types of radiation associated with them, a typical case of radio-active change will be considered, illustrating the phenomena exhibited by different radio-active substances, and showing how the Disintegration Theory put forward by Rutherford and Soddy offers a rational explanation of some of the fundamental facts of radio-activity.

Uranium is a radio-active body possessing moderate photographic action. In 1900 Crookes showed that an active body could be separated from uranium by chemical means, which was many times more active photographically than uranium. To this new substance he gave the name uranium X.

Becquerel found that by adding barium chloride to the uranium solution and then precipitating the barium, the uranium solution became almost inactive photographically, while the barium precipitate became very active.

The two parts were, however, kept for a year, when it was found that *the uranium had completely regained its activity, while that of the barium had completely disappeared*.

By a somewhat analogous procedure Rutherford and Soddy found that an intensely active body could be separated from thorium, to which they gave the name thorium X. As the result of a systematic examination of the phenomenon, it was found that the thorium X gradually lost its activity while that of the thorium gradually increased. At the end of a month the thorium X was no longer active, but the thorium had completely regained its activity. A similar series of observations by them

on uranium showed that the uranium X lost its activity according to a *simple exponential law,* the activity falling to half its initial amount in about 22 days; in another 22 days the activity was one-quarter, and so on.

These phenomena received a rational explanation by the Disintegration Theory of Rutherford and Soddy. For the case in question they suggested that part of the uranium had changed into uranium X, and that this body has a relatively short life.

The Disintegration Theory leads us, in attempting to picture radio-active processes, to realise how intimately the chemical and physical properties displayed by these bodies are bound up with the structure of their atoms. We are introduced to the conception of some inherent instability in atoms which prevents their being permanent: they change spontaneously into another kind of atom, which may be still more unstable. In this act of transformation either an alpha, beta or gamma ray is shot out from the atom; it loses some of its constituent parts, and the succeeding atom is of correspondingly smaller atomic weight.

The succession of changes of which uranium 1 is the starting-point will be briefly sketched on the lines laid down by the theory in question. The atoms of the element uranium are supposed to be unstable, and at any instant a very small proportion of them show this instability by shooting out alpha particles and instantly being converted into a totally different substance, known as uranium X_1. The instability has been handed on to these new atoms and to an accentuated degree; so much so, in fact, that in the course of a year nearly all the atoms of this body have shot out beta and gamma rays and been converted into a new body, uranium X_2. This is a still more unstable body, and is quickly transformed into the substance, uranium 2.

The instability now appears to have received a check, for uranium 2 is not very unstable; yet as time proceeds more and more of its atoms will have ejected alpha particles, thus transforming themselves into ionium, which is again slightly more unstable and changes into radium. With the advent of radium an even more surprising change occurs, for with the ejection of an alpha particle from its atoms it is thereby transformed into a gas, the so-called Radium Emanation.

Radium really changes spontaneously into *two* gases, for we have already seen that the alpha particles are really atoms of helium. The new member, the emanation, is more unstable than radium itself; it emits alpha particles, and its disintegrated atoms return to the solid phase; it is a new body, radium A, with quite definite physical properties and extremely unstable; in the course of a few minutes (about 30) after it has been isolated it can no longer very easily be detected; its atoms have ejected alpha particles and been converted into a slightly more stable body, radium B. The process continues with extraordinary fluctuation in instability, until it finishes with the formation of some stable type of atom with which our previous ideas were more reconciled.

Enough has perhaps been said to convey a meaning to the term radio-active change, and also to indicate what light has been shed on such obscure phenomena by the Disintegration Theory of Rutherford and Soddy.

TIME-PERIOD.

The time taken for the activity of a radio-active body to diminish to one-half of its initial value is known as the "Time-period." All the radio-active substances which allow of their rate of decay being measured have been found to follow an exponential law, and the importance of this law will be apparent from its far-reaching applications.

If we are given the amount of a radio-active substance whose time-period is known, this law allows an exact determination of the amount present at any subsequent time; and not only this, for, if in decaying it give rise to other radio-active bodies whose time-periods are known, similar information may be found relating to these bodies, this process being continuable in complicated cases where four or five bodies are simultaneously concerned, each with its characteristic time-period and type of radiation.

The time-period of a radio-active body is probably intimately bound up with the order of stability of its atoms. A comparatively stable body such as uranium will have a very long time-period, for its atoms are changing very slowly into UrX,

which is a much more unstable body, its time-period being a matter of a few weeks.

Among the 30 radio-active bodies known, there is an extraordinary range of instability, as indicated by time-periods which range from many millions of years, the estimated time-period of uranium to less than a millionth part of a second. Amazing as it may seem, it has been estimated that the time-period of one of the members of the thorium series is only of this duration.

THE CRITERION OF ACTIVITY.

It has already been stated that there is a wide range of activities in the various radio-active bodies; for example, radium is about two million times as active as uranium.

The activity of a body is inversely proportional to its time period, *i.e.* the shorter the time-period the more active the body. A body with a time-period of 1 minute, meaning thereby that one-half of it in this time will have been transformed into some other substance, will be 60 times as active as a body with a time-period of an hour. By this it is not meant that the first body would necessarily give effects 60 times as large as an equal weight of the second body, for the radiation emitted by the two bodies might be of two different types; nevertheless, the term "activity" is associated with the time-period in the manner indicated.

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CHAPTER IX

THE RADIO-ACTIVE EMANATIONS

IN 1900 Rutherford discovered that thorium compounds give rise to a gaseous product. This gas, which he named thorium emanation, was found to have the power of ionising gases and affecting photographic plates. When separated from the thorium compounds, as for instance by being pumped off from them, the emanation was found to lose its activity rapidly. The activity was measured by its ionising action upon the air in a vessel connected to an electrometer; the variation of activity with time, which Rutherford observed, may be seen from the numbers in Table 26. It will be seen later that the decline in its activity is due to the fact that the gas is spontaneously changed into another substance, which is not as radio-active as itself.

TABLE 26.

Time in Seconds.	Current.	Time in Seconds	Current.
0	100	155	14
28	69	210	6.7
62	51	272	4.1
118	25	360	1.8

Thorium emanation, apart from its radio-active properties, behaves like an inert gas of high molecular weight, and is condensed slightly above the temperature of liquid air. It is not actually given off from thorium, but from its derivative, thorium X, and in very minute quantities.

As this gas decays it gives out alpha particles, which account for the ionisation indicated above ; as the alpha particle is ejected from the emanation atom, the residue of the atom (*i.e.* the transformation product) is another radio-active body known as thorium A, which however is a solid. This body gives out alpha rays, and has a time-period of .14 second, and in turn gives rise to another body, thorium B, which gives out beta rays and is transformed into thorium C, which in turn gives rise to thorium D.

Subsequently to the discovery of this gaseous product from thorium compounds, it was found by Dorn that radium also produced a gaseous substance, and this gas was by analogy called radium emanation. In many respects it resembles thorium emanation, in that it has marked radio-active properties and behaves chemically as an inert gas of high molecular weight. Owing to the slow rate of change of radium, its emanation is only produced in small quantities, generally speaking far too small to be directly weighed. Its density has, however, been determined by Gray and Ramsay by collecting the emanation from nearly half a gram of radium and weighing it by means of an extremely sensitive micro-balance. Assuming it to be monatomic, the molecular weight was found to be 218.

As the emanation is continuously produced, the quantity of a sample of radium must necessarily diminish as time goes on. Actually this rate of transformation of radium into the emanation is exceedingly slow ; if a gram of radium were isolated, then, according to Rutherford's estimate, one-half of it would be transformed into the emanation in 1690 years.

From this illustration it will be seen that preparations of radium may be spoken of as constant radio-active sources, the loss of activity over a century being only about 3 per cent.

The transformation of one radio-active body into another is in all probability always accompanied by the emission of some kind of radiation from the body, the radiation being either of the alpha, beta or gamma ray type.

We have already seen that the alpha particles consist of positively charged helium atoms travelling with high speed ; the atomic weight of helium is 4, so it is clear that the expulsion

of an alpha particle must result in a diminution of the mass of the original radio-active atom. The case of radium may be taken as an example and represented diagrammatically in Fig. 10:

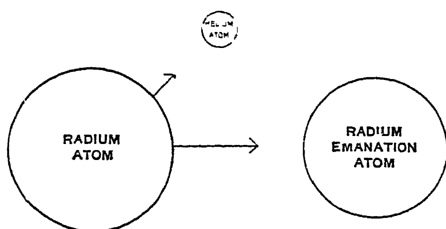


FIG. 10.

The disintegration theory predicts that the atomic weight of the radium emanation is 222.5. The experimental value obtained by Gray and Ramsay is very nearly this number.

The beta rays consisting of high-speed electrons, the mass of which is negligible, the emission of this type of radiation leads to no appreciable diminution in the mass of the radio-active body, and yet equally important atomic changes are associated with such an emission as in alpha particle radiation. Similar considerations hold for the cases of gamma radiation.

THE SOLUBILITY OF RADIUM EMANATION.

In common with most other gases, the emanation goes into solution when brought into contact with liquids. It has been shown to follow Henry's law very exactly; that is to say, that the amount of emanation absorbed by any particular liquid is proportional to the pressure of the emanation. The extent to which the emanation goes into solution is usually expressed by the term "coefficient of solubility," which is defined as follows: Let the volume of liquid be V_1 in contact with a volume of gas V_2, and let the quantity of emanation distribute itself between them, so that after equilibrium is established E_1 is the quantity of emanation contained in the liquid and E_2 the quantity in the gas. Then $\frac{E_1}{V_1}$ is the concentration of emanation in the liquid, and $\frac{E_2}{V_2}$ the concentration in the gas. The ratio of these two quantities, namely, $\frac{E_1}{V_1}\Big/\frac{E_2}{V_2}$, is the "coefficient of solubility." For example, if a bulb contain equal volumes of air and water at normal temperature and pressure, then any emanation contained in the bulb will distribute itself so that its concentration

in the air is about 3.3 times the concentration in the water, *i.e.* the "coefficient of solubility" in the water is $\frac{1}{3.3} = .30$.

The "coefficient of solubility" depends upon the temperature, as may be seen from the data in Table 27, which are taken from the accurate determinations which have been made by R. W. Boyle.

TABLE 27.—COEFFICIENT OF SOLUBILITY OF RADIUM EMANATION IN WATER AT ATMOSPHERIC PRESSURE.

Temperature.	Coefficient.	Temperature.	Coefficient
0 C.	.506	20.0 C.	.245
4.3	.424	26.8	.206
5.7	.398	34.8	.176
10.0	.340	35.2	.170
14 0	.303	39.1	.160
17.6	.280		

It will be seen that at body temperature (37° C.) the coefficient has a value about .165, about one-half of that at ordinary room temperature. The solubility of the emanation in physiological saline, .9 per cent. (such as would be used for injections into the human body) is slightly less than in distilled water.

Some organic liquids absorb the emanation to a very large degree. A selection is made in Table 28 of three such liquids whose coefficients have been determined by Boyle.

TABLE 28.

Liquid.	Coefficient of solubility at 14° C.	Absorbing power compared with that of water at 14° C.
Absolute alcohol - -	7.34	24.2
Amyl alcohol - - -	9.31	30.7
Toluol - - - -	13.7	42.2

When radium emanation mixed with air is breathed, it will, by solution and diffusion, gradually make its way into the circulation, and thence into the system generally.

The "Emanatorium," which has been largely used in parts of Europe for therapeutic purposes, consists essentially of a closed chamber, the atmosphere of which contains a measured quantity of radium emanation. In certain forms of treatment the air is breathed for quite long periods (2–3 hours), and in this way it is claimed that the emanation gradually permeates the system.

Some exhaustive observations have been made by Ramsauer and Holthusen upon the extent to which the emanation goes into solution in the circulating blood under the conditions detailed above. Using the term "coefficient of absorption" in the sense already made use of, they found that at 37° C. this coefficient for radium emanation and the circulating blood varied between the normal limits .29 and .32. Extreme values were .224 in a case of anaemia and .367 in a case of polycythaemia.

The same authors were led to a determination of this coefficient for some constituents of the blood, and obtained the following values:

TABLE 29.

Substance.	Coefficient at 37° C.
Distilled water - - - -	.163
Physiological saline (.9 per cent.) -	.148
Blood serum - - - - - -	.168
Citrated plasma - - - -	.175
Red corpuscles in physiological saline	.298

They also found the time required before there was equilibrium of the emanation throughout the system, and the rapidity with which the emanation escaped when the patient was removed from the radio-active atmosphere. The following table shows that in about half an hour after entry into the emanation atmosphere the equilibrium quantity of emanation had gone into the system, and that one hour after removal into fresh air it was reduced to less than 10 per cent. of this value.

The emanation, being carried by the circulation throughout the body, will continually be forming the active deposit, which is not lost by way of the lungs, as is the case with the emanation.

TABLE 30.

Time after entry into emanation atmosphere	Percentage of the maximum value absorbed.
0 minutes	0
37 „	94·7
120 „	101
197 „	100

Time after removal from emanation atmosphere.	Percentage of the maximum value absorbed.
0 minutes	100
10 „	44·3
30 „	21.3
60 „	8.4

CONDITIONS FOR OBTAINING RADIUM EMANATION.

Radium emanation is produced directly from radium; if the radium preparation is in the form of a powder, such as the carbonate, the emanation as it is formed remains occluded in the grains, and is only expelled by heating. The best way to obtain the emanation from radium is to dissolve the preparation in water or dilute hydrochloric acid, and connect the containing vessel to an ordinary mercury pump; the emanation, as it is

TABLE 31.—GROWTH OF RADIUM EMANATION FROM RADIUM.

Days.	Percentage of Final Value (100).	Days.	Percentage of Final Value (100).
1	16.50	10	83.51
2	30.28	12	88.52
3	41.77	14	91.91
4	51.37	16	94.41
5	59.39	18	96.10
6	66.09	20	97.28
7	71.68	24	98.67
8	76.18	30	99.55
9	80.25		

formed, may then be easily collected over mercury. A solution of a radium salt, when "pumped off" in this manner, immediately begins to grow more emanation, which collects until an equilibrium value is reached corresponding to the particular quantity of radium there is present. Tables 31 and 32 show the gradual growth of the emanation from radium and its decay when separated from its parent substance. The method of measurement of the emanation is considered in Chap. XI.

TABLE 32.—THE DECAY OF ACTIVITY OF RADIUM EMANATION WHEN SEPARATED FROM RADIUM.

Days.	Percentage of initial activity.	Days.	Percentage of initial activity.
0	100	9	19.7
1	83.5	10	16.5
2	69.7	12	11.5
3	58.2	14	8 0
4	48.6	16	5.6
5	40.6	18	3 9
6	33.9	20	2.7
7	28.3	24	1.3
8	23.6	30	.45

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CHAPTER X

THE ACTIVE DEPOSIT OF RADIUM

A VESSEL containing radium emanation is found to be radio-active after the emanation has been completely pumped out of it. This is due to the deposit upon its walls of a solid substance which is produced by the emanation, and which has received the name of Active Deposit. In reality it is not a single substance, but consists of a number of quickly changing radio-active bodies, which will be considered in some detail.

The emanation emits alpha particles only, and is thereby transformed into a *solid body*, called radium A, which is a very quickly changing body, having a time-period of 3 minutes. RaA emits alpha particles, and is transformed into another body, RaB. This substance has a time-period of 26 minutes, emits beta and gamma rays, and is transformed into RaC, which has a time-period of 19 mins., and emits alpha, beta and gamma rays in changing to RaD. The series of changes continues still further, but RaD is a comparatively inactive body, having a period of 16.5 years, and followers in the series are also bodies of slow change.

The three bodies RaA, RaB, and RaC together are known as the active deposit of quick change.

When reference is made in the text to the active deposit of radium, that of quick change is meant.

From the foregoing considerations it will be seen that the active deposit is generally present with the emanation. If the emanation be led into a vessel, it immediately forms some RaA, which, behaving as a solid, is partly deposited on the walls of the vessel, and gives rise to RaB, etc.

Rutherford observed that the active deposit makes its way to

a negative electrode, and may in this way be obtained in a very concentrated form. An Active Deposit is also formed from the emanation of thorium and of actinium.

A convenient method of obtaining an "active wire" is illustrated in Fig. 11.

The emanation, when pumped off from a radium solution or preparation, is collected over mercury in a glass tube *T*. The inside of the tube is fitted with a piece of wire gauze *G*, which makes electrical contact by means of the mercury with the positive pole of a battery of cells or the mains. A wire *W* of platinum or steel is threaded through a bent piece of glass tubing, sealed at *S* and introduced into the space containing the emanation. It is then joined to the negative pole of the battery, preferably through a water resistance to avoid a short circuit. The emanation is itself uncharged, but RaA that is formed from it has a positive charge, and therefore goes to the negative electrode, where it is deposited.

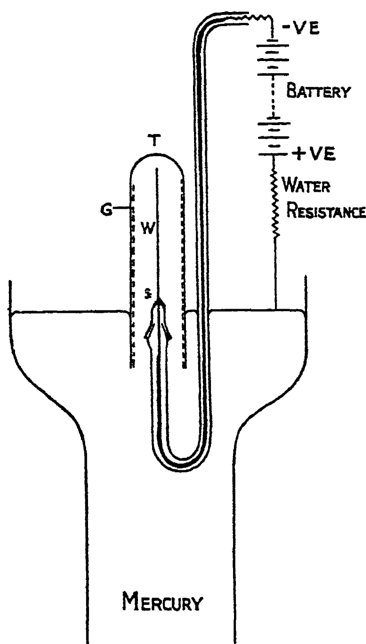


FIG. 11.

With a field of several hundred volts per cm. a large percentage of the active deposit may be dragged to the central wire *W* as soon as it is formed. The RaA deposited on the wire decays to form RaB, which in turn forms RaC; these remain on the wire, and eventually a condition of equilibrium obtains when the maximum amount of active deposit is obtained. This is about 3 hours after the exposure of the wire has begun. The active deposit adheres to the wire, but may be dissolved off by strong acids.

The radiation from such an active wire is complex, consisting of alpha, beta and gamma rays.

The activity of these wires is of comparatively short duration,

the decay of activity being different according to which type of rays is measured. This is clearly seen from the data in Table 33, which correspond to two different conditions of measurement, the time of exposure being the same in the two cases.

TABLE 33.

DECAY OF RADIO-ACTIVE DEPOSIT.

Alpha Rays.		Gamma Rays.	
Time.	Activity.	Time.	Activity
0 mins.	100	0 mins.	100
10 ,,	53	10 ,,	96.6
20 ,,	46	20 ,,	88.4
30 ,,	40	30 ,,	—
40 ,,	35	40 ,,	66.9
50 ,,	30	50 ,,	—
60 ,,	26	60 ,,	38.5
1 h. 30 ,,	14	1 h. 30 ,,	25.3
2 h. 00 ,,	7.2	2 h. 00 ,,	12.9
3 h. 00 ,,	1.8	3 h. 00 ,,	3.1

Wires which can be made exceedingly active in the manner detailed may be of clinical use, as shown by C. R. C. Lyster and Russ. Their use is naturally indicated in positions to which access is difficult. There is some advantage in their use, as the total radiation from the active deposit may be utilised without having suffered any absorption from a containing receptacle.

We may now consider what happens when some emanation is pumped away from a solution of radium and sealed off in a glass tube.

Initially there is only the emanation present, which gives out alpha particles and produces RaA. These alpha particles are unable to penetrate the walls of the glass tube, so that we should at the outset be unable to detect the presence of the emanation by means of an electroscope, the radiations being entirely confined within the glass tube. The RaA which is formed, also emits only alpha particles in being transformed to RaB: with the production of RaB the conditions are changed, for in its transformation to RaC beta and gamma rays are emitted, some of

which penetrate the walls of the glass tube with consequent detection by the electroscope. As radium C is formed, it in turn decays with the expulsion of alpha, beta and gamma rays; the beta radiation entering the electroscope is thus reinforced, and gamma radiation superimposed. The intensity of the gamma radiation simply depends on how much RaB and RaC is present in the glass tube; their amount reaches a maximum just about 3 hours after the emanation has been let into the tube. When this is so, there is a condition of equilibrium existing between the emanation and the active deposit produced from it; there are just as many atoms of the emanation changing into RaA per second as atoms of RaA changing into RaB—hence the amount of RaA remains constant, also there are just as many atoms of RaA changing into RaB per second as atoms of RaB changing into RaC—hence the amount of RaB remains constant, and so on. This condition of equilibrium, however, is but momentary, for the first member of the series, the emanation, is not a constant source, but is slowly decaying.

Considerable clinical use has been made of the emanation, in the first instance, we believe, by the Radium Institute, London. The gas is sealed in glass tubes, and the above considerations show that 3 hours after a tube is sealed the radiation is the same as if the tube were filled with radium itself, except for the absence of the radium, which itself gives out rays, but in small quantity. Joly and Stevenson have succeeded in using the emanation when it is sealed in glass tubing so thin that it may be inserted in an ordinary hypodermic needle; its insertion into growths thus becomes much simplified, and the beta rays are largely utilised. Such tubes gradually diminish in intensity. The data in Table 32 show the intensity at various times after equilibrium is first reached.

From the foregoing considerations it will be seen that when the emanation is in equilibrium with the radium producing it, there is also the condition of equilibrium existing between the radium and the active deposit.

We are now in a position to appreciate how it is that measurements of the amount of radium or of the emanation may be made by means of the gamma rays, although the gamma rays that are utilised are not produced by either of these substances, but by RaB and RaC.

Suppose that a glass tube containing a weighed quantity of pure radium bromide be mounted at a measured distance from an electroscope, and that a screen of lead about 3 mm. thick be interposed between the radium and the electroscope; then, since no beta rays can penetrate this thickness of lead, the only rays that enter the instrument are the gamma rays. They will produce an ionisation which causes the gold-leaf of the instrument to fall, and this may be registered as so many divisions per minute of the scale in the eye-piece of the instrument.

An exactly similar procedure may be adopted when dealing with quantities of the emanation, and by a comparison of the number of divisions passed over per minute by the leaf, the quantity of emanation may be expressed as the quantity in equilibrium with a definite quantity of pure radium. In this connection the unit known as the "Curie," page 88, may be referred to.

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CHAPTER XI

METHODS OF MEASUREMENT OF RADIUM

WHEN quantities of radium of the order of a milligram and upwards are in question, the usual method adopted is to compare the ionisation caused by the gamma rays from it, with that caused by the gamma rays from a known standard. This is conveniently done in the following manner. The tube containing the radium is placed at a definite distance from a gold-leaf electroscope (*vide* Fig. 12) whose walls are of lead, at least 3 mm. thick, which ensures that only gamma rays can enter it. The gamma rays from the sample in question ionise the air within the electroscope, and the extent of such ionisation is measured by the number of scale divisions in the eye-piece of an observing tele-microscope which the gold-leaf passes over in a given time. A large number of such observations is made, and the mean value of the number of scale divisions per minute taken; the standard is now placed in the position previously occupied by the sample, and a corresponding set of observations made. The rate of fall of the gold leaf is proportional to the amount of radium present. Without any radium being present, however, it is found that the gold leaf falls very slowly, this being due to the spontaneous ionisation of the air, and this is termed the "Natural Leak" of the inst-ument; it varies with the particular instrument em-

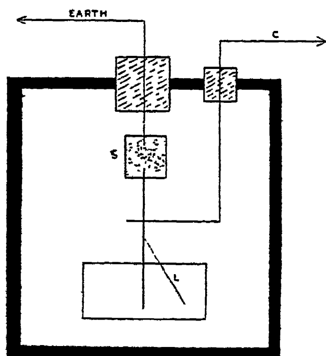


FIG. 12.

ployed, and in a reliable one is usually not more than .2 or .3 of a division per minute, and may even be less.

Some idea of the sensitiveness of an instrument such as is depicted in Fig. 12 may be obtained if it is stated that the gamma rays from 50 milligrams of radium bromide, when placed 100 cms. from the instrument, would cause the gold leaf to fall at the rate of about 50 divisions per minute. Under such circumstances it will be seen that the natural leak of the instrument comes in as a very small correction.

A few experimental points in connection with the instrument may be mentioned. The gold leaf hangs from a thin brass support, which is fixed to the sulphur plug *S*; this insulates it from the vessel, which is itself connected to earth. The gold leaf is given an electrical charge, by connecting it by means of the wire *C* to a battery of cells or a small electrostatic machine, such as C. E. S. Phillips has devised for the purpose; when the charge has been given to *L*, the wire *C* is swung out of position, so as to touch the wall of the vessel, and thus become earthed. When the charge is dispelled from the leaf by the ionised air, the procedure is repeated.

It is generally found that on first charging the instrument the readings are not so consistent as is the case when readings are repeated some hours later; this is attributed to the gradual soaking in of the electrical charge into the sulphur plug; the effects vary according to the size of the plug used. Phillips has overcome the difficulty by maintaining the leaf at the highest potential required, so that the instrument is always in a condition suitable for accurate use.

Samples of meso-thorium are usually stated to have a gamma ray activity equivalent to so many milligrams of radium, and measurements on this substance are accordingly carried out in the manner described.

It is clear that such measurements would not distinguish between meso-thorium and radium, but samples of pure meso-thorium can be distinguished from those of radium by two methods. The average penetrating power of the gamma radiation from new preparations of meso-thorium is less than that from radium, as Hahn has recently shown by a series of measurements in which the gamma rays were gradually absorbed by increasing thicknesses of lead. Another method depends on the

fact that the gamma ray activity of radium preparation is almost entirely confined to the two products RaB and RaC; consequently, if a tube containing the material be opened, thus allowing the emanation to escape, the gamma ray activity may fall to a small fraction of its original value, especially if the tube be heated to drive off the emanation. This reduction of activity would not be nearly so pronounced in the case of a preparation of meso-thorium, for although some of its gamma ray activity is due to ThC and to ThD (Table 14), about an equal amount is due to meso-thorium itself, which would remain in the tube.

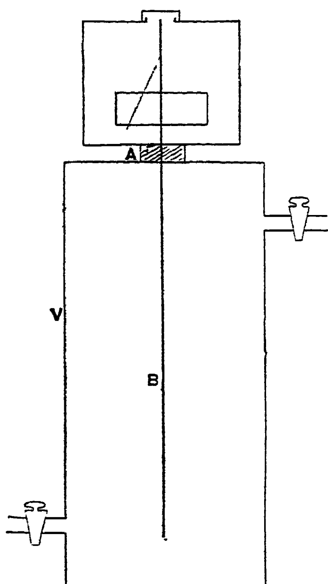


Fig. 13.

It frequently happens that quantities far less than a milligram are under measurement, as, for instance, in determining the amount of radium present in springs, in natural deposits, or in artificially prepared radio-active waters.

The usual method adopted in these cases is to measure the ionisation produced by the alpha rays emitted by the emanation and its products. It will be remembered that the ionisation in an electroscope caused by the alpha rays from a body like RaC is several thousand times as great as that caused by its gamma rays, hence the adoption of alpha ray measurements when very small quantities are being dealt with.

If the radium is in solution, a measured volume is put into a flask, boiled to expel the emanation, and sealed. If radium is present the emanation will be formed from it, and will accumulate in the flask, increasing in quantity, as shown by the numbers in Table 31. After any desired interval the flask is connected to an emanation electroscope (Fig. 13), and boiled to drive off the accumulated emanation.

The instrument is seen to consist of two parts: the top part consists of a simple type of gold-leaf electroscope; the rod carrying the gold leaf being continued through a sulphur plug *A*,

serves as an electrode *B*, lying along the axis of a large cylindrical vessel *V*, which is provided with an inlet and outlet pipe, the latter allowing the exhaustion of the vessel, the former the entry of the emanation. The gold-leaf system being charged, some of the ions produced by the alpha particles emitted from the emanation are drawn to the electrode, and gradually neutralise the charge on it, which is indicated by a gradual fall of the gold leaf in the upper system.

The alpha ray activity continues to increase after the entry of the emanation into the vessel, owing to the production of RaA, RaB, etc., the maximum activity being reached after about 3 hours.

This maximum value, if compared with that from the emanation in equilibrium with a known amount of radium, allows of quantitative measurements being made.

With an instrument of the above type, exceedingly small quantities of radium can be detected. There is little difficulty in measuring to a fair degree of accuracy quantities of the order 10^{-10} gram, *i.e.* one ten-millionth part of a milligram, of radium, and smaller quantities can be detected; the limit of detection with this type of instrument is 10^{-12} gram.

THE STANDARD OF RADIO-ACTIVE QUANTITY.

While the ionisation method, by virtue of its wide range of applicability, is of great use in all comparative measurements of radio-active bodies, it cannot easily be utilised as a basis of measurement which will serve as a standard of radio-active quantity. It will appear later that the quantities of these bodies with which we have to deal are usually very small, and in many cases far beyond the possibility of detection by the balance. Under these circumstances it is a matter of difficulty to decide as to the nature of the standards to be adopted.

In the case of radium itself the quantities usually involved are of the order of milli or centi-grams, and therefore directly measurable by a good balance. Provided the preparation is pure, there is no difficulty in a definite statement being given as to the amount of radium present.

Mdme. Curie and Debierne having separated radium in the metallic state, it was decided at the Brussels International Con-

gress for Radiology and Electricity, 1910, that a 20 mgms. standard of pure radium should be prepared, together with subsidiary standards, to ensure that accurate measurements may be made of any preparations. The National Physical Laboratory is in possession of a subsidiary standard, which is called the British Radium Standard, and official measurements of radio-active substances are carried out by that Institution.

For many scientific and therapeutical purposes, accurate quantitative measurements of radium emanation are very important, and the above Congress decided upon the name " Curie " for the amount of emanation in equilibrium with one gram of radium (element).

This quantity is very large for most purposes, and the terms milli-Curie and micro-Curie have come into general use for quantities of emanation corresponding to 1 mgm. and .001 mgm. respectively.

A practical unit by which quantities of radium emanation are compared is the Mache unit. This unit corresponds to an exceedingly small quantity, one Mache unit being only equal to 4×10^{-10} curie, or 4×10^{-7} milli-curie.

This unit has been much abused by its too general use. It was originally introduced by Mache, so that the very small quantities of emanation found in springs, rivers, etc., could be specified simply. For example, a weak radio-active spring will have an emanation content of about 10 Mache units per litre, or 4×10^{-9} curie, a moderately strong one about 100 Mache units, and a thousand of such units is occasionally recorded for natural springs.

The use of the Mache unit in cases other than that for which it was originally intended is to be deprecated, especially as it may, to the uninitiated, give the impression that large quantities are involved when in reality the reverse may be the case.

In practice the measurement of quantities of radio-active substances in the solid form is nearly always made by comparing their gamma ray activity with that of a standard by means of an electroscope or electrometer.

The reason for this, as will appear later, is that only a very small fraction of the gamma rays is absorbed by the receptacle (glass or metal) in which the substance is contained. This is

not so for the alpha or beta types of radiation, and consequently great care has to be taken when accurate comparisons of the alpha and beta ray activities of different substances are required.

Radium forms various salts, some of which, such as the chloride and bromide, are easily soluble ; others, such as the carbonate and especially the sulphate, are much less so. In the purchase of radium it should be borne in mind that the value of a preparation is simply proportional to its radium content ; owing to the fact that pure radium is never prepared, the commercial article is one of the various salts. The relative proportion of radium in these salts will be seen from Table 34.

TABLE 34.

Salt.	Percentage of Radium.
Radium Bromide, $RaBr_2 . 2H_2O$	53.6
Radium Bromide Anhydrous, $RaBr_2$	58.6
Radium Chloride, $RaCl_2 . 2H_2O$	67.9
Radium Chloride Anhydrous, $RaCl_2$	76.1
Radium Sulphate, $RaSO_4$	70.2
Radium Carbonate, $RaCO_3$	79.0

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CHAPTER XII

THE OCCURRENCE OF RADIUM IN NATURE

The discovery of radium in the pitchblende residues soon led to the examination of many other mineral deposits, and although there are few places where it is found in considerable quantities, it is not a little remarkable that it is one of the most widely distributed substances; in fact, there are few places where the presence of radium cannot be detected, whether it be in volcanic rocks or the ocean waters.

For the measurement of the quantity of radium present in ordinary sea or river waters a certain refinement of apparatus is necessary, but in other cases, notably some of the spring waters, there is no difficulty in establishing its presence.

It is an interesting fact that many of the spa waters contain radium in considerable quantities, but whether the beneficial effects associated with spa treatment are at all to be attributed to the absorption into the system of radio-active substances, is not likely to receive a satisfactory answer until definite curative action is proved with radio-active waters, free of the many salts which are present in most of the spa waters.

To give some idea of the quantities in which radium occurs in different deposits, reference may be made to Tables 35 and 36, which contain some of the results obtained by various observers. In most of the rocks the emanation is in equilibrium with the radium. In the case of waters, however, this is frequently not so; more emanation is sometimes found in the surrounding atmosphere than in the fluid itself. Under suitable experimental conditions the emanation can usually be detected in the atmosphere.

The data for the Bath waters are due to Ramsay, and the

measurements of the Buxton waters were made by Makower. The waters do not contain as much radium as their emanation content indicates. As the water passes through the soil the emanation may be taken up into solution without the radium.

TABLE 35.

Source	Observer.	Quantity of radium
Igneous rocks - -	Strutt	Mean value 4.7×10^{-12} gr. per gr.
Sedimentary rocks -	Strutt	,, 1.1×10^{-12} ,,
N. Atlantic Ocean -	Eve	,, .3 to 1.5×10^{-12} grams per litre.
Atlantic Ocean - -	Knocke	,, 17×10^{-12} grams per litre
Ocean waters - -	Joly	Ranging from 2 to 34×10^{-12} grams per litre

TABLE 36.

Spring Waters.	Millicuries per million litres.
BATH—	
King's Well water - - - -	1.73
Cross Bath waters - - - -	1.19
Hetling Bath water - - - -	1.70
King's Well gas - - - -	33.65
BUXTON—	
Hospital Natural Baths water - -	.83
Crescent Pump-room water - -	.83
Gentlemen's Natural Baths water -	1.1
Buxton natural gas - - - -	7.7–8.5

H. W. Schmidt and Kurz made an elaborate examination of over a hundred natural springs in various parts of Germany, from which they concluded that the presence of radium emanation (and occasionally thorium) could be detected in the majority of such springs and in considerable amount in some cases.

These observers report that the amount of emanation found

depends very largely on the local geological formations. Very small amounts were obtained from a soil of chalk or sand.

There was, however, no obvious connection between the amount of emanation found and the potency of such waters from the point of view of spa treatment, some of the most celebrated spas having amongst the lowest recorded emanation content. For further details of this series the original memoir should be consulted.

Measurements by Satterley of the amount of radium emanation in the atmosphere near the earth's surface at Cambridge have provided the following data. The average radium equivalent per cubic metre is 105×10^{-12} gram, the lowest value recorded being 35×10^{-12} gram, and the highest 350×10^{-12} gram. The emanation contained in the air of certain soils has been measured by Satterley in Cambridge, by Joly in Dublin and by Sanderson in Newhaven, U.S.A. This has been done by letting the air come up from various depths of soil by means of pipes. The very concordant results of these observers show that there is much more emanation in the soil air than in the atmosphere. Satterley states that for depths of 100–150 cms. in gravelly soil the amount is on the average 2000 times as much as there is usually to be found in atmospheric air. The fact, recorded by Elster and Geitel, that the air in caves usually contains more emanation than is found in the external air, is in accordance with these observations.

Thorium is also a very widely distributed element, and its emanation is to be detected in the atmosphere. It is never found at a great height above sea-level, however, because, owing to its short time-period (p. 46), it will have changed into its active deposit before it has had time to diffuse to a very appreciable distance.

Our normal habitat then seems to be a radio-active one. Whether this condition has any appreciable effect upon the animal economy is difficult to determine. It is safe to say that most of the recognised biological effects of the rays from the radio-active substances have been observed when dealing with concentrations several millions of times greater than occur in nature.

With such a general distribution of radium, the question arises as to its presence in the animal and vegetable kingdom.

Lazarus-Barlow has shown that the presence of radium can be demonstrated in human tissues by means of electroscopic measurements; as anticipated, the quantities are small. He gives as the mean value for three normal human livers 8×10^{-12} grams radium per 100 grams of material. From the preceding table it will be seen that this is about 1/50th of the mean value for igneous rocks. Lazarus-Barlow has raised the question whether the radium content of tissues is different when such tissues are the seat of malignant disease. The data he has so far obtained lead him to believe that tissues which are the seat of malignant disease contain more radium than such tissues under normal conditions.

Of 25 normal tissues examined he gives as the mean content 1.1×10^{-12} grams radium per 100 grams of material, whereas 7 samples of non-cancerous tissues in cases of malignant disease had a mean content of 23.6×10^{-12} grams per 100 grams. Investigation of 3 cases of metastases and 12 of primary growths gave values 55.3 and 51.6×10^{-12} grams per sample, the weight of material not being stated, but probably it did not exceed 100 grams.

Such data are very difficult to obtain under strictly comparable quantitative conditions, especially in view of the very small quantities which are involved (never as much as 10^{-10} gram Ra per gram of material).

Caan in 1911 showed that the introduction of dried preparations of tissues into a Wolff electrometer caused an accelerated discharge of electricity from the system. The largest effect was obtained from brain substance, and was equal to that from 3×10^{-9} gram of radium per gram of tissue. This effect, however, was not proved by Caan to be due to radium as in the experiments by Lazarus-Barlow.

Measurements were made in 1905 by Paul Becquerel to see whether plants contained appreciable quantities of radio-active material. He concluded that if they did contain any radium, it was in such minute amount as to have no effect upon their development.

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PART II

CHAPTER I

CHEMICAL ACTION

RADIUM.

It is interesting to note that the earliest recognised phenomena of radio-activity were due to the chemical action of the rays. In 1896 Becquerel made the fundamental observation that the rays emitted from uranium were capable of affecting a photographic plate in such a manner that although previous to development the plate was apparently unaltered, yet when the plate was developed, it was seen that an effect had been produced apparently identical with that caused by exposure to light.

Effects of radium and its emanation upon simple chemical compounds. Among the elementary substances which are affected by exposure to radium rays are certain of the metals, notably mercury, aluminium and lead, which all undergo oxidation, a phenomenon in which the alpha rays play by far the most important part. Of considerable practical importance is the fact that platinum is attacked by radium salts in solution.

The action of radium and its emanation upon different simple chemical compounds has been made the subject of study, notably by Curie, Debierne, Giesel, Ramsay, Soddy and Cameron. In the case of aqueous solutions of radium bromide, a partial decomposition of the water into hydrogen and oxygen has been found to occur, and the amount of this decomposition has been variously given by different observers. Thus for 1 gram of radium bromide acting upon water, Curie estimated that .2 c.c. of electrolytic gas (mixture of hydrogen and oxygen) was evolved per hour, while for identical conditions of quantity and time, Debierne gives .54 c.c. and Ramsay .32 c.c.

Radium emanation. The action of radium emanation upon water, carbon monoxide, carbon dioxide, hydrochloric acid gas, ammonia, and steam at 130° C. has been studied by Ramsay and Cameron. The only instance in which the emanation was without apparent effect was that of steam at 130° C. In all the other cases effects mainly destructive, but partially also synthetic, were observed. Thus water was found to undergo a partial decomposition into hydrogen and oxygen; carbon dioxide breaks down into carbon, oxygen and the monoxide; carbon monoxide yields carbon and oxygen, but here there is also evidence of a slight degree of synthesis, for carbon dioxide is also produced; ammonia is decomposed into nitrogen and hydrogen, and hydrochloric acid yields hydrogen and chlorine.

To demonstrate the synthetic effects of the emanation, the same observers also exposed mixtures of nitrogen and hydrogen. and of oxygen and hydrogen to its action; in both cases a small amount of combination was observed. The rates of decomposition and of synthesis have been shown to follow an exponential law, but, as stated previously, for the same quantity of emanation the phenomena of decomposition are much more prominent than are those of synthesis.

The beta rays. The beta rays have been found by Debierne and by Kernbaum to effect a decomposition of water which results in the formation of hydrogen peroxide and hydrogen. Becquerel noted that these rays could change ordinary yellow phosphorus into the allotropic red variety, and it has been shown by Hardy and Willcock that they liberate iodine from a solution of iodoform in chloroform.

A synthetic action of the beta rays was noted by Jorissen and Ringer in the case of hydrogen and chlorine, which combined to form hydrochloric acid.

An examination of the action of beta rays upon certain photosensitive solutions was made by Flaschner, and he came to the conclusion that the action was similar to that of light.

Effects of radium and its emanation upon more complex bodies. An interesting observation upon the effect of the emanation is due to Orlow, who found that paraffin wax, which is so highly resistant to ordinary chemical reagents, was affected by it, becoming hard and brittle and acquiring a brownish tinge. Other substances, such as spermaceti, bees-wax, and certain of the

higher fatty acids, also underwent change apparently of an oxidative character. Liquid paraffin, when exposed to the emanation, suffers a darkening of colour and becomes opaque.

Lecithin. This has been the subject of many experiments, and some early observations of Schwarz upon the action of radium rays on this body led him to the conclusion that it underwent decomposition as the result of the exposure. These findings were apparently confirmed by Schaper and Werner. Thies, however, although he exposed lecithin to radiations of nearly four times the intensity of those used by Schwarz, failed to detect any specific alteration, a finding which was confirmed by Hertwig. In all experiments with lecithin, it must be remembered that it is a particularly unstable body, and readily undergoes spontaneous change merely as the result of exposure to air. The question of the action of radium and its emanation upon lecithin has, however, more than a mere academic interest. Since lecithin is so constantly found as a constituent of the animal cell, the upholders of the view that it was especially sensitive to radium regarded this as explanatory of the destructive effects of radium upon the tissues. Quite apart from the question of the precise conditions under which lecithin may exist in the living cell, which may be quite different from those obtaining "*in vitro*," it may be said that no conclusive evidence of lecithin destruction in a living cell has been brought forward. To assume that it is the lecithin of the cells which is attacked, and that as lecithin is a constituent of practically all cells, therefore the products of lecithin decomposition account for the damage produced by irradiation, is clearly illogical, since the same argument might equally be applied to the water which is also universally present in the cells.

Monosodium urate. Observations upon this substance were first made by Gudzent in connection with researches upon the effect of "emanatorium" treatment of gout and allied disorders. He claimed that the monosodium urate in the blood of such patients was broken up by radium D (see p. 44) into several simpler bodies, which were eventually eliminated as carbon dioxide and ammonia. The action of radium emanation upon monosodium urate *in vitro* was subsequently investigated by Mesernitzky. He found that, working with a concentration of .5 millicurie per c.c., after 12 days' exposure .029 gram of the monosodium urate was decomposed by 50 millicuries. In no

"emanatorium," however, would there be more than one-millionth of a millicurie per c.c., *i.e.* 2500 Mache units; so that under the emanatorium treatment the concentration in the blood of the patient is about one ten-millionth of that with which Mesernitzky worked, it therefore seems unlikely that the decomposition of monosodium urate in the blood by this means can have any appreciable clinical significance.

Colloids. Hardy's experiments upon globulin solutions. If samples of globulin are obtained from ox-serum, and two solutions prepared, one rendered acid by the addition of dilute acetic acid, and the other alkaline by means of ammonia, in both cases the solutions become opalescent, but the colloidal particles of globulin have acquired fundamentally different characters in the two cases. In the acid solution they carry a positive electrical charge; while in the alkaline solution the charge carried is negative. Such solutions are known as "electro-positive" and "electro negative" respectively.

Hardy's experiments consisted of two series. In the first series the acid and alkaline solutions were exposed in small cells (one side of which was in each case made of mica) to 50 mgs. of radium bromide contained in a suitable capsule and covered with a thin piece of mica. This mica cover was placed in contact with the mica wall of the cells containing the solutions under investigation. No change was observed in either solution even after an hour's exposure.

In the second series, samples of both these globulin solutions were exposed as naked drops in proximity to the radium. In three minutes changes were apparent; for, while the acid solution became clearer (showing thereby more complete solution), the alkaline solution turned to an opaque jelly.

Now, in the first set of experiments, where the radium and the globulin solutions were separated by two layers of mica, the alpha rays were cut off, and only the beta and gamma rays could reach the solutions. When, however, the naked drops were directly exposed close to the radium, the alpha particles were also enabled to reach them, and hence the phenomena observed must clearly be due to them. The explanation of the difference of the behaviour on the part of the two solutions is that in the case of the alkaline solution the positive charges carried by the alpha particles neutralised the negative ones carried by

the globulin particles, which latter were accordingly precipitated. When, however, the globulin particles carried a positive charge, the effect of the positively charged alpha particles was to cause a more complete solution.

This result is of the highest importance, as showing that exposure to alpha radiation may produce results which differ not only in degree but in kind from those caused by exposure to the beta and gamma rays.

Analogous experiments to those of Hardy were done by Henri and Mayer, who worked with colloidal solutions of silver and of ferric hydrate. In these cases the colloidal silver particles are negatively charged, and the ferric hydrate positively. These were exposed to the radiations from .1 gram of radium bromide enclosed in a thin glass tube. A four-days' exposure led to no apparent result. To each solution was now added a trace of sodium nitrate solution, but in quantities so small as to be by themselves incapable of producing precipitation. On now re-exposing these "sensitised" solutions to the radium, the silver solution remained intact while the ferric hydrate was precipitated. The action here is attributed to the negatively charged beta radiations.

Some observations were made by the present authors, by exposing serum, and nucleo-albumin prepared from the thymus gland, to radium emanation, but a diminution in the viscosity of the solution was the only change observable; no chemical alteration was detected. With solutions of starch the result was different, as a portion was converted into dextrin and a still larger proportion into "soluble starch."

In 1915 and 1917 Fernau and Pauli published the results of their work upon the action of radium on colloids. For this purpose 220 mgr. of radium carbonate were sealed in a glass tube 1.1 mm. in thickness, so that 80 per cent. of the β radiations and 1 per cent. of the γ were absorbed. The liquids and suspensions were examined in small flat bottomed test tubes in each of which about 2.5 c.c. were placed, along with the little tube of radium carbonate.

Suspensions of coagulated albumen and sols of well dialysed native proteins were employed. The suspensions were examined in the presence of acetate mixtures of varying hydrogen-ion concentration, and it was found that both on the acid and alkaline

sides exposure to the radiations caused agglutination of the suspensoid matter. On native proteins irradiation caused irreversible changes tending to coagulation, a lowering of the coagulation temperature and increased tendency to precipitation by alcohol. Unlike the suspensions of coagulated protein, in which the tendency to agglutination by radiations is accelerated by the presence of salts, sols of native albumins are protected.

A further series of observations was made upon colloidal solutions of ceric hydroxide, prepared by dialysis of solutions of ceric ammonium nitrate. Upon keeping, these sols spontaneously undergo changes, such as a diminution in viscosity, a gradual loss of the tendency to gelatinize and a diminution in their sensibility to the action of electrolytes. It has been suggested that these changes are due to dehydration of the sol particles.

If ceric hydroxide sols are exposed to the β or γ radiations from radium, the first obvious change is an initial diminution in viscosity. This however is succeeded by a marked increase, the viscosity becoming greater than that of the non-irradiated material. The progress of the second stage is not dependent upon a continued exposure to the rays, since when this was intermittent the course of the viscosity-time curve was found to be unaltered.

When the exposure to radiations was stopped before the end of the first stage (*i.e.* during the lessening of the viscosity) a rapid onset of the second stage occurred, the viscosity increased and attained a maximum which was followed by a diminution in viscosity almost as rapid as the increase before the attainment of the maximum.

Upon sufficiently prolonged irradiation the changes in the sol lead to the production of a stable gel.

Changes similar to those described above are also produced by the action of electrolytes. If an amount of electrolyte (insufficient to cause immediate coagulation) is added to ceric hydroxide sol, there is an immediate initial diminution in viscosity,—the viscosity next increases and finally a gel is produced. If the amount of added electrolyte is smaller, the initial diminution in viscosity is followed by a rapid increase to a maximum, which in turn gives place to as rapid a diminution.

The viscosity-time curve is therefore very much like that occurring after exposure of the ceric hydroxide sol to β or γ rays; but differs in that the upward and downward limbs

of the curve on the two sides of the maximum are much steeper when the curve expresses the result of exposure to radiation. The gel produced by the action of electrolytes is unstable, it becomes turbid, contracts and sets free water, while, as previously noted, the gel produced by exposure to radiations is stable.

Generally speaking the phenomena associated with the "ageing" of sols are supposed to be due to the formation of larger colloidal particles as a result of aggregation and to be associated with alterations in the degree of hydration. Probably the elements of the disperse phase in sols of ceric and other metallic hydroxides possess a high degree of hydration and thereby differ from those of metallic or sulphide sols. Under the influence of electrolytes or of β or γ radiation the electrical charges of the elements of the disperse phase are altered, which results in a diminution in the degree of their hydration, with an accompanying diminution in the viscosity of the sol. This change is gradual when it results from irradiation, but rapid or immediate when an electrolyte is added. The increased viscosity noted in the second stage is probably due to the aggregation of electrically neutral particles.

The peculiar change resulting from a short exposure to the rays or the addition of a small quantity of electrolyte—namely the attainment of a maximum viscosity and its subsequent fall—are more difficult to explain. The suggestion put forward is that it is due to the presence of electrically charged colloidal particles enclosed in a jelly resulting from the aggregation of electrically neutral particles. As a confirmation of this may be mentioned the fact that ceric hydroxide gel can be rapidly "peptized" by the addition of its corresponding sol.

Enzymes. The most diverse statements have been made concerning the action of radium rays upon these bodies. To take pepsin as an example; Bergell and Bickell claim that its activity is increased, Miss Willcock finds it diminished, while London states that no effect whatever is produced by exposure to radium. Miss Willcock also found destructive effects in the case of trypsin and ptyalin; Henri and Mayer, in emulsin and trypsin. Rennin was found by Miss Willcock to be unaltered, but Schmidt-Nielsen detected a slight destructive effect. Discrepancies like these appear at first sight inexplicable, but the following considerations may throw some light upon them. Enzymes such as trypsin, pancreatic amylopsin and pepsin do

not exist as such in the cells of the secreting glands, but in a zymogen or prozymogen stage. These zymogens and prozymogens are themselves inactive, and in an extract from a digestive gland at first preponderate largely over the fully formed enzyme. If, for instance, an extract of pancreas be made, it will be found, on keeping it, that its digestive activity rises gradually until it attains a maximum, and then loss of activity gradually supervenes. Moreover, the rate of development of activity and the stability of the extract when made depend not only upon the condition of the gland but upon the medium used for the preparation of the extract. In certain of the experiments made upon the action of radium on enzymes, such considerations may help to explain the varying conclusions of different observers, since the zymogens and prozymogens are in general much more resistant to noxious influences than are the fully formed enzymes themselves. Moreover, it is quite a tenable hypothesis that exposure to the radium rays might accelerate the conversion of zymogen to enzyme, while at the same time exerting a prejudicial effect upon the enzyme when formed. It can be seen that under these conditions an extract composed mostly of zymogen would appear to be activated while one in which the zymogens had been already converted into enzymes would have its activity diminished. A somewhat analogous thing occurs in the case of pancreatic extract, where the addition of a trace of dilute acid accelerates the conversion of inactive zymogen to active enzyme, but very rapidly destroys the formed enzyme unless speedily neutralised. Similarly, it is a well-known fact that trypsin itself acts best in a faintly alkaline medium ; at the same time, however, it more rapidly undergoes deterioration in an alkaline than in a neutral solution. Vernon has carried out a most extensive series of researches upon the pancreatic enzymes ; in these he investigates the effects of different media (glycerol, dilute glycerol, dilute alcohol, etc.) for preparing these extracts, and also the relation of the activity of the extract (*i.e.* conversion of zymogen to enzyme) to the length of time it has been prepared.

It is therefore probably not too much to say that, until experiments upon lines similar to those performed by Vernon are carried out with irradiated and non-irradiated samples, we shall still have confusion and discordant results.

Miss Willcock exposed extracts containing tyrosinase to the

beta and gamma rays from 50 mgr. of radium bromide for periods varying from two to four days, but was unable to detect any change in its activity. More recently Marshall and Rowntree have exposed lipase to radium emanation, but no alteration in its activity could be noted.

Autolysis. The effect of radium emanation upon autolysis has been made the subject of enquiry by Löwenthal and Edelstein. Generally speaking, they found an increased autolysis as the result of exposure to radium emanation; this increase, however, was found to vary very much with the character of the material allowed to autolyse. The most marked increase was found in the case of human cancer tissue, where an enormous increase was found to occur; while mouse cancer, on the other hand, actually showed a slight diminution. Again, in autolysis it must be remembered that we are not only dealing with a highly complex series of intracellular enzymes, but that the condition of the cells themselves has also to be taken into account.

That the condition of the cells themselves is of importance is shown by the following experiment. As is well known, the cells of the kidney are very rich in an enzyme, or enzymes, known collectively as erepsin, which acts upon peptone so as to break it down into its constituent amino-acids. Now, if a fresh kidney be perfused with saline solution, the liquid as it issues from the organ will be found to contain practically no erepsin. If, however, a solution of chloroform be made in a similar sample of saline to that used in the first experiment, and the perfusion repeated, it will be found that the issuing fluid now contains erepsin in considerable amount. The explanation is probably to be found in the fact that some disintegration of the cell is necessary for the liberation of the enzyme, and this means of disintegration is supplied by the tissue-poison chloroform. Similarly, if kidney tissue be very finely minced, ground up with sand, and finally mixed with kieselguhr and submitted to the action of a powerful press, the issuing juice readily undergoes autolysis when placed under suitable conditions. Here again there has been a marked disintegration of the cells, in this case of a mechanical character. As will be seen later, radium has a powerfully destructive effect on many tissues, which will probably in some cases influence the rate of autolysis. The majority of the experiments upon the action of radium and its emanation on autolysis have been carried

out with finely minced tissue; here there is initially only a relatively small amount of mechanical cell disintegration, and it is impossible to say how far any effect produced by irradiation is due to the action of the rays upon the cells themselves, and how far it is due to their action upon the intracellular enzymes. What seems desirable towards elucidating this complicated problem is the preparation of non-cellular tissue juices as described above, and a study made of the subsequent autolysis of irradiated and non-irradiated samples. Such experiments conducted upon extracts made from various tissues whose normal autolytic degradation products are known, might also be of value in determining whether or not the rays have any selective action upon different intracellular enzymes, and hence form a basis for the investigation of the effect of radiation upon the bio-chemistry of the cell.

Venoms. Physalix investigated the action of radium and its emanation upon cobra and viper venom. He unfortunately does not mention the amount of radium or of emanation used, but the exposures were made for periods varying from fifty to sixty hours. The irradiated samples were then found to be innocuous when injected into frogs.

Chemical effects of α particles and electrons. The chemical reactions produced by the action of α particles and electrons have been dealt with at length in a special monograph by Lind to which the reader is referred for a detailed account.

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CHEMICAL ACTION OF X RAYS.

From time to time various substances have been submitted to the action of the X rays with a view to determining what chemical or physical changes were produced. In many cases the exposure is apparently without any effect ; in others physical or chemical changes follow irradiation.

Water. Prolonged radiation appears to have no effect, for Kernbaum exposed flasks of water to the X rays for 100 hours without producing evolution of gas or other alteration.

The platinocyanides. The action of X rays upon these substances is of interest, since the resulting changes are, in the case of barium platinocyanide, used to determine the dosage of the rays in clinical practice.

The first observations upon the subject are those of Villard, who, in 1900, showed that barium platinocyanide under the influence of X rays lost its natural green colour and fluorescence, and acquired instead a dull gold colour. The same observer also noticed that a sample of the salt which had undergone such a change as the result of irradiation could gradually regain its colour when removed from the influence of the rays. This recovery he erroneously attributed to the action of light.

The subject received further attention at the hands of Bordier

and Galimard, who thought that the initial colour change and loss of fluorescence under the influence of X rays were due to dehydration, and that the recovery of tint and fluorescence were due to rehydration. Levy however considers that the change of colour is due to a change from the crystalline to the amorphous condition. In addition to the barium salt, the platinocyanides of magnesium, ammonium and potassium were also found to undergo colour changes as a result of irradiation, and to recover their normal tints in the same way as barium platinocyanide.

The colour changes produced are shown below.

TABLE 37.

Platinocyanides of	Before exposure.	After exposure
Magnesium - - -	Vermilion	White
Ammonium - - -	"Old Gold"	Yellowish rose
Potassium - - -	Greenish white	Yellow ochre
Barium - - - -	Green	Dull gold

Iodoform. Hardy and Miss Willcock have shown that iodoform when dissolved in chloroform and exposed to the X rays undergoes decomposition with the liberation of free iodine.

Inorganic colloids. Bordier and Galimard have shown that a colloidal solution of phosphorus suboxide (P_4O) undergoes precipitation upon irradiation, leaving the supernatant ether quite clear.

Organic colloids. We owe the first note as to the action of X rays upon organic colloids to Bordier and Galimard These observers in the course of their investigations upon the action of X rays upon the incubating hen's egg noticed that the "white" of such eggs underwent a marked diminution in viscosity as a consequence of irradiation. In 1912 the present authors exposed nucleo-albumin, which had been prepared from the thymus, egg white and ox serum to X rays for several hours, and in all cases a diminution in viscosity was observed, but no other change could be detected. In the case of starch, however, irradiation produced a very definite and easily determined alteration.

Starch. Solutions of starch were exposed in Petri dishes covered with thin mica to the rays from an X-ray bulb, which

was run under conditions giving a moderately soft type of rays. After periods of irradiation ranging in various experiments from 2–8½ hours, a marked diminution in the viscosity and a decrease in opacity were observed. *The iodine reaction.*—The control and irradiated solutions both gave a deep-blue colour with iodine. No reduction was obtained on boiling with Fehling's solution or with alkaline safranin in the case of either the control or experimental fluid, showing that no conversion into reducing sugar had taken place.

Precipitation by electrolytes.—It has been shown by Young that starch and some of its early cleavage products are precipitable by certain electrolytes, among which are sodium sulphate and ammonium sulphate.

1. When a saturated solution of sodium sulphate is added to a solution of starch and left standing for some hours, it precipitates the ordinary starch, but not soluble starch or dextrin.

Accordingly samples of the control and irradiated solutions were saturated with sodium sulphate and allowed to stand for some hours. A marked difference was observed in the two cases.

The control showed a well-marked precipitate while the irradiated solution gave only a small precipitate and remained turbid.

After centrifugalisation, the supernatant fluids were pipetted off. That from the control solution gave no coloration with iodine, the irradiated giving a deep-blue colour. This showed that a portion of the starch had been converted into soluble starch which is not precipitated by sodium sulphate.

2. A saturated solution of ammonium sulphate, when added to an equal volume of starch solution (*i.e.* half-saturation) and left for a few days, precipitates all the starch and any soluble starch present, but has not this action on dextrin.

To see whether this substance has been formed in the irradiated fluid, samples of the control and irradiated fluids were taken, and to each was added its own volume of a saturated solution of ammonium sulphate. After being allowed to stand for two days the filtrates were examined. In the control no coloration was obtained on the addition of iodine, while the irradiated portion gave a port-wine colour indicating the presence of erythrodextrins.

The procedure just detailed for the detection of dextrin in the irradiated starch solution was carried a stage further in order to obtain some idea of the percentage change occurring in the starch.

After irradiation for 8½ hours the dextrin formed in the solution was separated from the starch and the soluble starch in the manner indicated. The ammonium sulphate remaining in the filtrate was got rid of by dialysis. This was continued for several days until no precipitate was obtained with barium chloride, thus showing the complete absence of ammonium sulphate. The pure dextrin left was evaporated down and weighed. Starting with 15 c.cm. of starch solution (4 grams in 250 c.cm. of distilled water), which contained 0.24 gram of starch, the dextrin obtained after irradiation weighed 0.0108 gram. Hence nearly 5 per cent. of the starch had been converted into dextrin. Owing to the intermediate formation of soluble starch, this indicates that a considerably larger percentage of the starch had been altered.

Enzymes. Bordier and Galimard have concluded that the X rays are without effect upon peptic digestion. Mayer and Bering found a slight diminution in the activity of peroxidase after one hour's exposure ; the same preparation, however, when exposed to the mercury quartz lamp for a quarter of an hour was completely inactivated. The proteolytic enzyme of yeast juice underwent a slight amount of damage as the result of strong irradiation, and the same was noted with the enzymes of pancreatic extracts. Autolysis, according to the same observers, is somewhat increased ; they regard this as due to a direct action of the rays upon the nitrogen-containing autolysable contents of the cell. Günther was unable to find any effect upon the following ferments when they were exposed for periods of about one hour at a distance of 12–14 cms. from the anode of an X-ray bulb giving a powerful discharge : pepsin (pur. pulv. solub. Merck), trypsin (pur. Grübler), pankreatin-glycerine (Grübler) and ptyalin. Lawrence (1922) found that X rays were without action upon the diastatic enzyme of urine, serum and plasma.

Vitamins. The action of X rays upon vitamins was investigated by Weill and Mouriquand. These experimenters worked with barley, batches of the seed being exposed to the X rays,

while samples of each batch were afterwards placed under conditions favourable to germination. Three batches of seed received doses of 50, 100, 150 Holzknecht units respectively. Of these, those receiving 50 H. appeared to exhibit a slight stimulation of the germination process. In the 100 H. batch, germination was impeded, and in the 150 H. batch it was either markedly inhibited or absent. Pigeons were fed on the irradiated samples of grain, since from their extreme sensitiveness to beri-beri it was considered that they would prove the most convenient test-animal. None of the birds so fed developed the slightest symptom of beri-beri; while if these birds are fed upon barley sterilized by heat, symptoms appear from the 25th to the 35th day.

There is, however, a variety of beri-beri which is extremely slow in manifesting its presence, requiring from 250 to 300 days, and in view of this the authors prefer not to make an absolute statement on the subject. When the extreme sensitiveness of the pigeon is taken into consideration, it seems certain, however, that exposure to X rays has no appreciable effect upon the vitamin, ("B vitamin") deprivation of which produces beri-beri.

On the other hand according to Plimmer this vitamin is destroyed by radium emanation.

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CHAPTER II

CERTAIN FORMS OF ANIMAL LIFE

RADIUM.

THE effect of radium rays upon certain low forms of animal life was made the subject of an interesting series of observations by Miss Willcock in 1904. Three capsules containing respectively 50, 10 and 5 mgs. of radium bromide were used, and the animals were exposed in one of two ways ; either they were suspended in hanging-drop preparations over the radium, in which case the alpha, beta and gamma rays all had effect : or they were placed in shallow cells fitted with floors of thin mica, over the radium capsules ; in this case only the beta and gamma rays were effective.

Protozoa. (1) *Euglena.* A large variety of *Euglena* was first used. At the time of observation the organisms were congregated in dense clumps, there was no evidence of sporulation, and the encysted state was regarded as entirely due to unfavourable conditions. One of the clumps was exposed in a mica-floored cell over 5 mgs. of radium bromide, on the following day motile forms began to detach themselves and on the third day the whole clump was broken up. A control clump, put up at the same time as the experimental samples, showed no change. Similar experiments were conducted with the 10 mgs. and 50 mgs. capsules, and the results were the same as in the preceding experiment ; with the increased quantity of radium, however, the appearance of motile forms and the disintegration of the clump were accelerated. Control experiments were also carried out, to show that exposure to light took no part in the production of the phenomena.

In a second series of experiments a small and active form of *Euglena* was used, in order to ascertain whether the motile forms either sought or deviated from, the course of the rays. The

organisms were exposed as before in the mica floored cells, but in the present instance, a lead screen with a single small perforation was interposed between the capsule and the cell, thus allowing of the passage of only a narrow pencil of rays. The motile forms seemed entirely unaffected, and showed no tendency either to shun or to seek the path of the rays. *Euglena* is remarkably irresponsive to all kinds of stimuli.

(2) *Stentor viridis*. For the experiments upon *Stentor viridis*, 50 mgs. of radium bromide were placed upon a sliding substage of the microscope, while the stentors were contained in a mica-bottomed cell upon the stage itself. On shifting the substage, so that the creatures were in the path of the rays, contraction was noticed. With repeated exposures, however, there was a marked diminution in irritability and rapidity of response. For instance, one specimen, when exposed for the first time, showed contraction after 5 minutes' irradiation ; at the fourth exposure this response was only obtained after 35 minutes, while after the fourth exposure no response at all was obtainable.

Other specimens showed decided response ; of sixteen exposed over-night, examination the next morning showed that fifteen had moved out of the path of the rays, only a solitary specimen remaining in their track.

(3) *Opalina*. (4) *Nyctotherus*. (5) *Balantidium*. Specimens of these parasites were obtained from the intestine of the frog. They suffered no damage from a 24 hours' exposure to the beta and gamma rays from 50 mgs. of radium bromide, by which they seemed totally unaffected as regards either movement or vitality. This result is of considerable interest, since these organisms have been shown by Dale to be very responsive to chemical stimuli, *e.g.* dilute acids and alkalis ; their lack of response to radium rays is therefore not merely due to a sluggish habit resulting from a parasitic mode of life.

(6) *Actinosphærium*. One specimen only was available for purposes of experiment. On exposure to the beta and gamma rays from 50 mgs. of radium bromide, it appeared irresponsive, but died after an hour's irradiation with the pseudopodia extended.

Some experiments of Veneziani (1904) upon *Opalina ranarum* show that irradiation prolongs the life of these organisms outside the body of the frog. He employed a tube of radium-barium bromide (.1 gram), and kept the opalinæ in .5 per

cent. saline solution. The tube was immersed in the liquid in the experimental series, and a set of ten experiments agreed in showing a prolongation of life *in vitro* in the irradiated specimens. Thus, in one experiment, after the expiration of 48 hours, while the control specimens were all dead, the irradiated were alive, though their movements were slower than normal, and they were still alive even after 72 hours. Unfortunately neither the thickness of the tube nor any quantitative physical data other than the supposed amount of radium-barium salt are given.

Zülzer, in 1905, published the results of some experiments upon protozoa, which are interesting from the large amount of radium employed. The following account is taken from references to the work by Günther and Guyot. The radium capsule contained 1.8 grams of radium-barium bromide ; a sheet of mica 4 μ thick served as a slide upon which the organisms were placed in a drop of water, covered with an ordinary coverslip and sealed up by vaseline. Exposures were made by placing the slide upon the radium capsule. *Amœba limax*, *Arcella vulgaris* and *Difflugia pyriformis* were unaffected ; *Pelomyxa palustris* was killed in 15 minutes. *Actinosphærium eichhorni*, irradiated from above, in an open glass cell for 72 hours, were in some cases killed, in others damaged and showing degenerative changes in the nuclei. *Spirostomum ambiguum* was unchanged after 24 hours. *Paramœcium caudatum*, when irradiated in an open glass cell, was hardly affected by a 24 hours' exposure, but when irradiated, as described above, without access of air, it was killed in 3 hours.

Upon *Paramœcium bursaria* (a chlorophyll-containing form) irradiation had no influence on the power of cell-division, but in *Paramœcium caudatum* and *Actinosphærium eichhorni* (which do not contain chlorophyll) this power was inhibited ; in the case of a specimen of *Actinosphærium*, in which division had commenced previous to exposure, irradiation for 2 hours caused obliteration of all traces of division. *Delonysea palustris*, when first exposed, appeared to undergo a temporary stimulation ; its movements were more lively and the intracellular movements of the protoplasm were accelerated. Later, however, the organism became sluggish and died.

Hydrozoa. (1) *Hydra viridis*. Twelve experiments were performed with *H. viridis* ; the cells in which they were contained

were partially screened from the beta and gamma rays from 50 mgs. of radium bromide by lead diaphragms with a small aperture. For each observation one hydra was used, and was allowed to fasten itself to the mica floor of the cell; by means of the perforated lead diaphragm, it was thus possible to expose or screen the animal at will. Of the twelve specimens examined, nine moved out of the path of the rays, and on re-exposure again went to the screened part of the cell. Fresh specimens responded to the stimulus of the rays more rapidly than those which had been previously exposed; thus a fresh sample took from 15–30 minutes to move into shelter, while one which had been previously subjected to exposure took from 1–2 hours.

The three specimens which did not move away from the path of the rays were feeble specimens and remained exposed in an uncontracted state. After being thus exposed for 4½ hours, they lived for some days, apparently but little, if at all, injured. One specimen survived an exposure of 12 hours.

In order to determine whether any part of the animal was especially concerned in the response to irradiation, specimens were divided transversely and exposed in the mica-bottomed cells. It was then found that the "foot" end remained passive, while the oral extremity moved itself out of the track of the rays.

H. viridis and alpha rays. Specimens were exposed as hanging-drop preparations to the alpha, beta and gamma radiation from 50 mgs. of radium bromide. After an exposure of 1 hour their vitality was markedly diminished and in 2 hours they were dead. Since exposure to the beta and gamma rays alone (from the same quantity of radium bromide) produced merely a temporary response with no apparent after-effects, it is clear that this lethal effect is due to the alpha rays.

(2) *Hydra fusca.* With this species the results of exposure were entirely different. Twelve specimens were examined; of these eleven appeared paralysed and soon died without any attempt to seek shelter. The remaining sample moved away from the rays, but on re-exposure could not be induced to repeat the action, and died fully expanded in their track. In these experiments, as in those with *H. viridis*, the 50 mgs. capsule was employed.

Rotifera. These organisms were often observed in the water

when the other types were under examination. Throughout the experiments they exhibited no tendency either to seek or to avoid the rays.

An interesting feature of the foregoing experiments is that only the chlorophyll-containing organisms gave any response at all, other than injury or death. Thus *Hydra fusca* and *Actinosphærium* soon died, and disintegrated after a few hours; *Nyctotherus*, *Balantidium* and *Opalina* showed neither response nor injury.

Hydra viridis, *Stentor* and *Euglena* all showed marked response. In *H. viridis* and *Stentor* this response took the form of definitely co-ordinated movement to escape from the rays, while *Euglena* underwent a change from encystment to activity. The destructive action of the beta and gamma rays, moreover, is less marked in these chlorophyll- than in non-chlorophyll-containing organisms. The highly destructive action of the alpha rays is of considerable interest, while the fact that the beta and gamma rays do not merely act in general as a " stimulus " is shown by the want of response of such usually responsive organisms as *Opalina*, etc., while the usually irresponsive *Euglena* undergoes change from encystment to activity.

The decreasing responsiveness of *Stentor* and *Hydra viridis*, as the result of repeated exposure, finds a parallel in the observation of Gamble and Keeble that *Convoluta roscoffensis* (another chlorophyll-containing organism) loses its response to the stimulus of light as the result of too great exposure.

Annelids. Bohn investigated the action of radium upon certain annelids (1903). Phenomena analogous to those of " light-rigor " were observed; the amount of radium used was not stated. With *Kiefersteinia* and various species of *Eulalia* a lethargic state was reached in from 20 to 60 minutes, while other species of annelida required 2 hours. The cephalic tentacles of *Praxithea irrorata* were found to be extremely sensitive, as were also those of *Terebella*. The branchial tufts of other forms did not exhibit this sensibility. In *Lanice conchylegia* both tentacles and branchial tufts are inserted in the cephalic region: normally the tentacles are in a perpetual state of movement, searching for grains of sand, whereof to make the tube which the animal inhabits; after exposure to radium these tentacles become lethargic, and the anterior segments of the animal move aimlessly about as

though searching for grains of sand, which they are unable to feel. The observed phenomena suggest an anæsthetic condition of the integument.

Crustacea. The same observer (Bohn) also exposed specimens of *Daphnia* and *Asellus* to the rays from the same tube of radium, both the tube and the animals being placed in a small quantity of water. The *Daphniæ* survived for periods varying from 12 to 24 hours, but *Asellus* proved more sensitive, and paralysis commenced after an exposure of 2 hours.

Radium emanation (amount not stated) was found to have a lethal effect upon *Daphnia* and also upon certain species of ants.

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X RAYS ON CERTAIN FORMS OF ANIMAL LIFE.

The study of the effects of X rays upon protozoa has more than an academic interest, since many of these organisms have been found to be pathogenic in character. Some of the earliest, if not quite the earliest, observations upon this subject were made by Schaudinn in 1899. His observations have an especial value, since he not merely enumerates the specimens with which he worked, the results obtained in each case and the quantitative details regarding the duration and intensity of irradiation, but also gives details regarding the morphological characters of each species, and their possible bearings upon the reaction of each individual to the rays.

For the purposes of these experiments, the length of spark gap worked with was 10–12 cms., the tube being placed 20 cms. above the glass dishes containing the specimens. In order to eliminate shaking, and to facilitate examination, these dishes with their contents were placed upon the stage of a microscope

standing upon another table than that which carried the coil. During the actual exposures the tube of the microscope was withdrawn, being replaced when it was necessary to take an observation. In all cases the duration of the exposure was 14 hours, with short intervals to allow of examination of the irradiated specimens.

(*A*) **Rhizopoda.** Twelve different forms of rhizopod were investigated.

(1) *Labyrinthula macrocystis* (Cienk). This remarkably sluggish form showed no change whatever, either during or after the exposure.

(2) *Amœba princeps* (Ehrbg.). At first no alteration was observable; but after an exposure of 5 or 6 hours the movements were distinctly more sluggish. After 10 hours the organisms assumed a spherical form. At the end of 14 hours eight specimens out of thirty were dead, the remaining twenty-two recovering after 3 hours and apparently none the worse for their exposure. These twenty-two specimens were all found to be mono-nucleated: of the eight dead specimens, only three had survived disintegration sufficiently to permit of a microscopical examination; but all of the three were found to be multi-nucleated, thereby suggesting that the multi-nucleated forms are less resistant to the rays than the mono-nucleated.

(3) *Amœba lucida* (Gruber). This amœba showed itself highly sensitive towards the X rays. After 4 hours' exposure the specimens assumed a spherical form, imbibed water, and after 10 hours were completely disintegrated.

(4) *Pelomyxa palustris* (Greef). This, the largest of the fresh-water rhizopods, behaved precisely like *Amœba lucida.* The interesting feature about them, however, is the fact that the larger forms were much more sensitive and more readily killed than were the smaller ones. The large specimens had become globular after 3 or 4 hours' exposure, and soon afterwards underwent complete and sudden disintegration. The smaller examples showed contraction after at least 6 hours, while the smallest were not destroyed even by a 10 hours' exposure.

(5) *Trichosphærium sieboldi* (Schneider) is entirely unaffected, even by a 14 hours' exposure. It is, however, one of the least responsive of all forms of rhizopod to any form of stimulus.

(6) *Arcella vulgaris* (Ehrbg.). After 10 hours all the pseudo-

podia were withdrawn, and after 14 hours the protoplasm was entirely retracted within the shell as a globular mass. Two hours after the conclusion of the experiment, however, complete recovery had occurred.

(7) *Difflugia pyriformis* (Perty). Apparently quite unharmed.

(8) *Hyalopus dujardini* (Max Schultze). The pseudopodia were not withdrawn and no changes were observed.

(9) *Gromia oviformis* (Duj). An experiment with twelve specimens showed withdrawal of all pseudopodia after 6 hours. At the commencement of the exposure there was definite acceleration of the movements of the intracellular granules, which, however, became perceptibly slower after 2 or 3 hours. After 14 hours the protoplasm in the shells of four individuals had become quite globular in form, and soon underwent complete disintegration. On the following day all the remaining specimens were dead and disintegrated.

(10) *Polystomella crispa* (L.). Retraction of pseudopodia was seen after 6 hours. In the initial stages of the exposure acceleration of the motion of the intracellular granules was noted. All the animals survived, and a few hours after the termination of the experiment the pseudopodia were again extruded. All the specimens were mono-nucleated.

(11) *Acanthocystis turfacea* (Carter). This organism has a symbiotic messmate in the form of a brown alga. After 4–5 hours' irradiation, retraction of the pseudopodia occurred. At the conclusion of the experiment the symbiotic algæ had completely disappeared, but pseudopodia were thrust out again a short time afterwards.

(12) *Actinosphærium eichhorni* (Ehrbg.). As soon as 2 hours after exposure had begun, all pseudopodia were withdrawn. Six hours' exposure produced marked changes and vacuolation in the protoplasm, while at the end of 14 hours complete disintegration had taken place.

(*B*) **Sporozoa.** These parasitic forms were suffered to remain in their respective hosts, and together with them were subjected to irradiation.

(1) *Clepsidrina polymorpha* (Hammerschon). This form is parasitic in the intestine of the meal-worm, the larva of *Tenebrio molitor*. Ten meal-worms were exposed. In eight of them the parasites were unaltered, one contained dead parasites and in

the tenth no parasites were found. The meal-worms themselves seemed unaffected by the exposure.

(2 and 3) *Coccidium schneideri* (Bütschli) and *Adelia orata* (Schneider) occur parasitically in the intestine of the centipede (*Lithobius forficatus*), and exhibit no change as the result of a 14 hours' irradiation.

(4) *Karolysus lacertarum* (Labbé). This organism occurs in the blood of lizards, and after an exposure of 14 hours showed no alteration.

(*C*) **Flagellata.** (1) *Chilomonas paramœcium* (Ehrbg.). After a 6 hours' irradiation the animals became much less lively, and subsequently sank to the bottom of the dish. They tended to assume a globular form, and at the end of 14 hours were all dead and partially disintegrated.

(2) *Cryptomonas orata* (Ehrbg.). This form closely resembles the preceding, but differs from it in being more resistant, and in possessing two brown chromatophores. After 10 hours' irradiation their movements were very feeble and death soon supervened. After 14 hours, however, a few specimens were still alive; the chromatophores disappeared after 5–6 hours' exposure.

(3) *Euglena acus* (Ehrbg.). The specimens of this organism which were available for examination were all of the chlorophyll-free variety. After 8 hours the movements had become sluggish, and after 14 hours the creatures were all dead and lying on the floor of the vessel. There was no apparent granular disintegration, and the protoplasm seemed to have undergone no noticeable alteration. Two days elapsed before the dead cells were completely destroyed.

(4) *Oxyrrhis marina* (Duj). Oxyrrhis proved itself very sensitive to the X rays. After 2 hours it had assumed a more or less spherical form, and sunk to the bottom of the vessel. During the next 2 hours it remained perfectly still, and then suddenly underwent a violent disintegration in a similar manner to *Pelomyxa* among the rhizopods.

(*D*) **Infusoria.** Of the infusoria only one specimen was examined—*Spirostomum ambiguum* (Ehrbg.). The movements were clearly slower after an exposure of 4–5 hours. After 6 hours all the specimens sank to the bottom of the vessel and died in an extended condition. This result is noteworthy, since other

stimuli, such as shaking or chemical agents, cause strongly marked contraction.

Broadly speaking, Schaudinn found that those organisms with a more fluid protoplasm are the more sensitive, and as regards individuals of the same species the polynucleated forms are more easily affected than the mono-nucleated, while the parasitic forms which he investigated were unaltered. Observations by Kennon Dunham in 1904 upon a large variety of protozoa corroborate in the main those of Schaudinn, except that he did not produce a lethal effect upon *Cryptomonas* by the exposures he gave.

Günther, in a paper in 1909, reviews the experimental work which has been done previous to that date. The observations of Joseph and Prowazek in 1902 upon certain simple organisms, namely *Paramœcium caudatum* and *Volvox*, together with some *Daphniæ*, showed that exposure of these organisms resulted in their movement away from the direct stream of the radiation. Their results are, however, complicated by the temperature changes occurring in the fluid containing the organisms, for it is known that some forms of paramœcium are extraordinarily sensitive to small changes of temperature (.01° C.). These observers found that under irradiation the frequency of movement of the contractile vacuole was diminished.

With regard to trypanosomes, Günther states that their irradiation by X rays by Mense, Ross and Weber had yielded negative results. Löwenthal and V. Rutkowsky observed, however, that *Trypanosoma Lewisii* was very sensitive to these rays, whereas de Nobele and Göbel found that *T. Brucei* was quite insensitive to them.

With respect to malaria parasites, Demarchi was unable to detect any influence of the rays upon them.

Conflicting results have been obtained by Cowen, Scobbo, Laquerrière and Buschke upon the effects of X rays on the *Spirochæta pallida*; in some cases a positive and in others a negative result of such treatment having been recorded.

The results of Günther's own observations are summarised in the paper referred to above, and indicate that the protozoa examined by him are relatively insensitive to the rays.

He states, "With the intense radiation at our disposal with modern X-ray appliances, whereby a single exposure lasting 10 hours (and in all of 18 hours) has been made of cultures of

organisms placed 5 cms. from the bulb, no response or harmful effect has been observed upon irradiating *Paramœcium caudatum* (Ehrbg.), *Colpidium colpoda* (Ehrbg.), *Chilodon cucullus* (O. F. M.), *Urostyla grandis* (Ehrbg.), *Coleps hirtus* (O. F. M.), *Vorticella mikrostoma* (Ehrbg.), *Actinophrys sol* (Ehrbg.), *Gromia oviformis* (Duj), *Chilomonas paramœcium* (Ehrbg.), *Bodo oratus* (Duj) and *Trypanosoma Brucei.*"

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CHAPTER III

DEVELOPING FORMS

RADIUM.

Echinodermata. The ova and larvæ, in various stages of development of a sea-urchin, *Strongylocentrotus lividus*, were among the earliest forms to be experimentally submitted to the action of radium. This work was carried out by Bohn in 1903; he employed a tube containing "some centigrams" of pure radium bromide, and submitted the organisms to its action for varying periods. The normal development of this animal, as is usual among the echinodermata, presents three well-marked stages:

(1) The formation of a hollow ciliated sphere of cells, the "blastula" stage.

(2) The development of a digestive cavity, the "gastrula" stage.

(3) The formation of the "pluteus" larva, a form essentially characteristic of the echinoderms.

Exposures of blastulæ, for periods varying from 20 minutes to 2 hours, prevent them reaching the gastrula stage, and the ciliary movements become much less marked. Should the blastulæ at the time of exposure have already commenced to pass into the gastrula, the process is either stopped or proceeds irregularly; the digestive cavity, in such cases, being either markedly reduced in size or replaced by an irregular mass of cells. Gastrulæ, when momentarily exposed to the rays, generally developed to the pluteus form, but the larva in such cases was small, atrophic and atypical.

Ova and spermatozoa of the same sea-urchin were also exposed. In the case of the spermatozoa the result was rapid enfeeblement

and death ; ova, on the other hand, appeared to be more readily fertilised after irradiation, for some ova, which after fertilisation were able to exist long enough to proceed to a two-cell stage, when irradiated (previously to fertilisation) developed as far as a four- or eight-cell stage. In the last instance, however, the forms obtained were irregular.

On exposing non-fertilised ova a certain proportion (2–4 per cent.) underwent parthenogenetic division up to a certain point, but here again the forms obtained were irregular. Unfortunately in the experiments on ova and spermatozoa the times of exposure are not given, and as the amount of radium employed is recorded as "some centigrams," we cannot state the precise conditions which produced these apparently stimulating effects.

Nematoda. The ova of *Ascaris megalocephala* are so easily obtained, possess such a high degree of vitality and are so readily examined microscopically, that their development has been made the subject of various researches. Among the earliest were those of Perthes in 1904, when the action of both X rays and of radium was investigated.

Perthes employed three tubes, each containing 10 mgs. of radium bromide.

The ova were mounted as hanging-drop preparations, and the radium tubes placed on the upper surfaces of the coverslips for varying times. A delay in development was noted in all which had received at least a 2-hours' exposure ; in those which had only been exposed for 1 hour the first divisions were not delayed. Those irradiated for periods varying between 2 hours and 4 days did not in any instance proceed to the formation of a complete worm, many remained as irregular cell masses and underwent no further development. The damage done depends upon the length of exposure ; in the one-hour specimens a few attained normal development as complete worm embryos some exhibited monstrous forms similar to those produced by the X rays,* while yet others remained as irregular masses of cells. Here again radium, like X rays, does not effect the immediate death of the cell ; specimens subjected to three days' continuous irradiation still underwent division to form irregular cell masses although the process was markedly delayed, a four- or eight-cell stage being reached on the third day after exposure, when it ceased.

* See p. 136.

The action of very small quantities of radium upon these ova has been studied in great detail by Lazarus-Barlow and Beckton, who came to the following conclusions:

(1) If radium in quantities of the order 5×10^{-7} mgs. act upon these ova in the resting stage for a continuous period of about 30 hours at 0° C., cellular division subsequently proceeds at an accelerated rate.

(2) Greater quantities than the above or more prolonged exposures progressively retard the rate of division.

(3) These effects are brought about by the action of alpha, beta and gamma rays acting together.

When the alpha rays were cut out by suitable screens the quantity of radium had to be increased about 100 times to get the same effects.

The nuclear changes observed in the development of such irradiated ova have been investigated by Paula Hertwig. She employed three radium capsules, containing respectively 7.4 mgs., 5.3 mgs. and 2 mgs. The ova were spread out on cover-slips, previously smeared with agar to ensure adhesion; the radium capsules were supported just immediately above them, and during the irradiation (which lasted from ½ hour to 48 hours) the whole was kept in a moist chamber at a temperature of 16–21° C. After irradiation, fixation was effected by acetic alcohol, the specimens stained with Greinacher's borax carmine and differentiated in acid-alcohol. Sections prepared to exhibit the finer changes in the chromatin were stained by Heidenhain's method.

This series confirmed the retardation of development occurring as a sequel to irradiation. The centrosomes and spindle fibres were present in a normal manner, but destructive effects were noticed in the chromatin. The chromatin loop-formation ceased, and in place of it chromatin granules appeared; only in a few specimens—and those the less strongly irradiated ones—did an approximation to the loop-formation exist, but here the filaments on closer examination were seen to resemble strings of beads, indicating a marked tendency therefore to granule formation. At other times the chromatin presented the appearance of two compact plates in the middle of the spindle, but on suitable preparation even these could be resolved into closely compacted granule aggregates. Whatever effects radium may have on other

parts of the nucleus it undoubtedly has a markedly destructive action upon the chromatin.

These findings received independent corroboration from experiments conducted by Mottram, the chief aim of whose study was

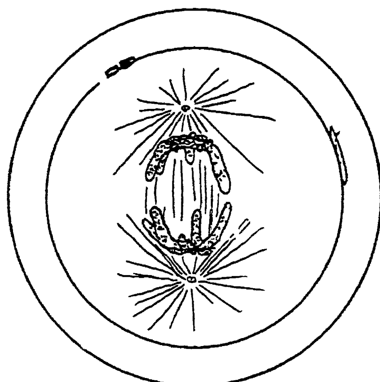


FIG. 14.

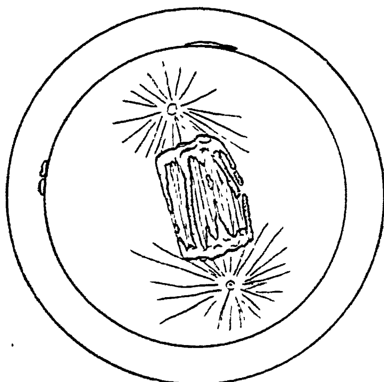


FIG. 15.

FIG 14.—A normal anaphase (side view). The chromosomes have split, and are emigrating towards the centrosomes along the spindle.

FIG 15.—An anaphase, showing irregularity in the splitting of the chromosomes; much of the chromatin has already migrated towards the poles, but at the equator a few granules still remain, and strands of chromatin connect the polar masses.

to find whether the various stages in the life cycle of the developing ovum showed, in any appreciable degree, changes in vulnerability to the same exposure of radiation. He exposed the ova in various stages of nuclear division to the beta and gamma rays from 7 mgs. of radium bromide, and found that they were about eight times more vulnerable if in active division than if they were in a resting condition during irradiation; this may be seen from the data in Table 36.

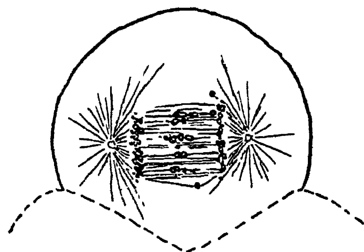


FIG. 16.—An anaphase, showing the irregular migration of the rods and granules to the poles; some have migrated, others are still at the equator.

Not only are the ova in the process of division especially vulnerable, but Mottram found that a stage during the process of division, namely, the metaphase, exhibited this vulnerability to a greater extent than any other phase; even here certain processes were found to be much more interfered with than others, for whereas no differences were

observed in the appearance of the centrosomes, attraction spheres or spindle, there were profound changes in the chromatin, consisting for the most part of irregular fragmentation, irregular migration of the fragments to the poles and crowding of the granules against the new cell wall.

TABLE 38.

Dividing Nuclei.		Resting Nuclei.	
Minutes exposure	Per cent of Ova killed.	Minutes exposure.	Per cent. of Ova killed.
1	10, 0	16	0, 0, 21
2	22, 12	24	38
3	16, 46	25	37
4	52	30	46
8	66	50	76, 40
10	96, 96, 99	150	100

Polychaeta. Investigations upon the action of radium rays on the development of *Nereis limbata* were made by Packard, whose general conclusions may be summarized as follows:

(1) Irradiated spermatozoa of *Nereis* react in two ways to the normal egg. They may either stimulate and be drawn into the egg in the usual manner; subsequent development is however wanting. Or they may fail to effect sufficient stimulation and consequently remain outside. In the first case the sperm nucleus and aster may fail to develop and fuse with the egg nucleus, while in the second case the egg nucleus develops without an aster.

(2) The irradiated egg, at the time of fertilization, may or may not extrude the cortical layer. In either case the maturation phenomena proceed abnormally and mitosis does not occur although the protoplasm may divide.

(3) Irradiation of the fertilized egg results either in non-fusion of the fully developed germ nuclei, or in abnormal divisions of the cleavage nucleus.

(4) Eggs irradiated either before or after fertilization show marked evidences of protoplasmic degeneration.

(5) Both protoplasm and chromatin are usually affected.

Redfield and Bright found marked thickening of the fertili-

zation membranes of *Nereis* ova as a result of exposure to the radiations from radium.

TABLE 39.

SHEWING THE DEVELOPMENT OF NEREIS EGGS IRRADIATED BEFORE INSEMINATION.

<table>
<tr><th>Minutes after Insemination</th><th>Normal.</th><th>Rapid β at 50 m m: 75 min. exposure.</th><th>Mixed β at 4 m m.: 90 min. exposure</th><th>Rapid β at 1 m m: 90 min exposure</th></tr>
<tr><td>10</td><td>Prophase.</td><td>Prophase.</td><td>Prophase.</td><td>Prophase.</td></tr>
<tr><td>20</td><td>Prophase.</td><td>Prophase: perivitelline space normal.</td><td>Prophase: perivitelline space normal.</td><td>Prophase: perivitelline space wide.</td></tr>
<tr><td>30</td><td>First metaphase at periphery.</td><td>Sperm entering: first anaphase.</td><td>First metaphase.</td><td>First metaphase.</td></tr>
<tr><td>35</td><td>Same: sperm still external.</td><td>First polar body extruded.</td><td>Sperm entering: anaphase.</td><td rowspan="4">Very abnormal development with suppression of the first polar body. In many cases the sperm does not enter.</td></tr>
<tr><td>40</td><td>Sperm entering. First anaphase.</td><td>Sperm in centre of Egg. Second metaphase.</td><td>Sperm entering. First anaphase. Perivitelline space wide.</td></tr>
<tr><td>45</td><td>First anaphase and telophase</td><td>Second anaphase and telophase.</td><td>Sperm in centre of egg. Abnormal polar divisions.</td></tr>
<tr><td>55</td><td>Sperm in centre of egg. Second metaphase.</td><td>Fusion of pronuclei.</td><td>A great variety of abnormalities.</td></tr>
<tr><td>65</td><td>Fusion of pronuclei.</td><td>Cleavage.</td><td>Cleavage rare.</td><td>Cleavage rare and abnormal.</td></tr>
<tr><td>75</td><td>Cleavage.</td><td></td><td></td><td></td></tr>
</table>

Mollusca. A series of upwards of forty experiments upon the eggs of a slug-like, marine gasteropod (*Philine aperta*) was made by Tur in 1909. Single exposures to 9 mgs. of radium bromide were given ; the duration of the irradiation varied from 6–20 hours, and the eggs were in different stages of development at the times of their respective exposures. No deviation from the normal could be detected up to the completion of gastrula formation ; subsequently, however, there was irregular cell proliferation, and the outlines of the embryos became abnormal and irregular. Later, marked irregularity of growth occurred in the cells of the endoderm ; relatively huge masses of cells were extruded, which for some hours remained attached to the larva by a more or less narrow pedicle, but subsequently became detached. This process is repeated, but despite this enormous loss of material, development still continues with the production of the " veliger " stage. The cilia are well developed and show a highly active degree of movement.

The extrusion of cells, either singly or in masses, continues without intermission, and the result is a marked diminution in the size of the " veliger," which is finally reduced to about one-third of its normal size. The ciliated portions appear the most insensitive to the deleterious effects of radium, and indeed at the sixth or ninth day, when the general body of the larva has been reduced to an irregular mass of cells, the ciliary movements persist without sensible impairment. The monstrous larvæ do not form mature animals, but die off when about nine or ten days old.

Tur's researches were extended later to *Pholas Candida L.*, the ova of which, when irradiated for periods of 6–24 hours by the rays from 9 mgs. radium bromide, exhibited unusual types of division ; there is, however, a gradual return to the normal process, but the resulting individuals were found to be very delicate. When the irradiation of the ova is very prolonged the process of division is profoundly disturbed, and may be described in the author's own words, viz. " tout à fait bizarre."

Fishes. The action of radium upon the unhatched embryos of the common dogfish (*Scyllium canicula*) was made the subject of observations by Tur in 1906. He used a tube containing some centigrams of a very active preparation containing about 35.1 mgms. radium chloride. The radium was placed immediately

over the blastoderm, the position of which was clearly ascertainable through the semi-transparent egg-case. The eggs were kept in a vessel of running sea-water and maintained in a vertical position. Only a single exposure to radium was given in each case, the duration varying from 66–70 hours, different eggs being irradiated at different stages of their development ; the controls were eggs from the same female as the experimentals. As a result of irradiation, it was seen that the embryos were smaller than the normals, and the axial parts were affected, the peripheral parts of the blastoderm being quite normal both in extent and appearance. There was no trace of a neural canal, the central nervous rudiments being reduced to a mere ectodermal plaque, which subsequently, along with what would normally have been the protovertebræ, was reduced to an agglomeration of rounded cells which in places exhibited necrotic changes. The endoderm also showed similar changes.

Amphibia. The ova, spermatozoa and larvæ of frogs, toads and newts have been made the subjects of experiments by many observers, among whom may be mentioned Bohn, Schaper and the Hertwigs.

Bohn's observations, published in 1903, were performed with the same tube of radium bromide, containing "some centigrams," as he used in his experiments with the larvæ of the sea-urchin. As material he used frog and toad tadpoles in different stages of development. The exposures lasted from 3 to 6 hours, and were made by placing the animals in a small dish with a little water on which floated the glass tube containing the radium bromide.

Toad tadpoles normally develop very slowly for the first ten days after emergence from the egg ; eighteen specimens of different ages, exposed to radium as described, underwent a retardation of growth. With frog tadpoles (whose normal rate of development is much greater than that of the toad) the result was different. Of thirty-eight specimens subjected to irradiation, nine died almost immediately, and the remainder behaved differently, according as they were younger or older specimens. Upon individuals eight days old the exposure had an immediate effect, the external gills rapidly disappeared, and the skin became irregularly nodulated and folded, so as to produce monstrous forms. In younger examples, on the other hand, exposure to

radium had no obvious immediate effect, but they subsequently developed into monsters in the same way as the older specimens.

Further experiments upon frog and newt tadpoles were made by Schaper. He employs 10 mgs. of radium bromide contained in a mica-covered capsule. The duration of exposure varied from 1½ to 30 hours. Like Bohn, he found the rate of development arrested, and curious monstrosities with nodulated integument were produced, which did not live to reach the adult form.

After Schaper's death his collection of specimens was subjected to a careful examination by Levy, whose results may be briefly stated as follows :

(1) In the period of cleavage of the ovum, irradiation may check or inhibit cell-division while producing no obvious cell degeneration. Death may ensue as a result of such exposure.

(2) In the later stages of differentiation of the organs many degenerative abnormalities may occur ; these are especially marked in the neural tube, retina and olfactory organs. On the other hand, the optic lens, pigment layer of the retina, aural vesicle, chorda dorsalis and myotomes exhibit but little change. The heart remains rudimentary while the tubules of the pronephros are dilated. The severe effects of irradiation are most marked in those structures where growth and complex differentiation are most rapid.

(3) In still later stages the primary effect appears to be mainly upon the blood vessels.

A most exhaustive and interesting series of experiments upon the influence of radium on amphibian development was carried out by O. and G. Hertwig. The papers are so complete and detailed that it is impossible in a short account to do justice to them, and consequently in the following note only the very broadest outlines can be sketched. Throughout the researches the same three capsules of radium bromide were used ; these contained respectively 7.4 mgs., 5.3 mgs. and 2 mgs.

The experiments of O. Hertwig fall into two groups. In the first group he irradiated normal fertilised frog ova in the early stages of development ; in the second, normal unfertilised ova were artificially fertilised with irradiated spermatozoa, which were either obtained from the seminal vesicles, or by reducing the testicle to a pulp with a little saline solution.

Series (A). *Irradiation of normal fertilised ova.* In this case there is a marked retardation of the developmental processes. The formation of the gastrula is retarded, as is also that of the medullary groove and its subsequent closure to form the neural canal. The larvæ did not attain maturity, but sooner or later died as monstrosities. The deleterious effects of the radium rays were especially noticeable in the nervous system where cellular destruction, pigmentation and irregular proliferation occur. In addition, the development of the heart and processes connected with blood formation are interfered with and proceed irregularly. The integuments present marked changes, showing irregular foldings, nodulations and warty excrescences. Such modified tadpoles show a marked disinclination to movement, and usually lie in a dull and lethargic condition.

Quantitative experiments upon the effects of irradiation of already fertilized ova showed that the destructive changes varied with the amount of radium and the duration of exposure.

Series (B). *Fertilisation of normal ova with irradiated spermatozoa.* In this series of experiments a remarkably interesting phenomenon was observed. If the spermatozoa were irradiated for varying periods up to 60 minutes, and then used for impregnating normal ova, development proceeded abnormally and irregularly, and the degree of abnormality attained ran nearly parallel to the amount and duration of irradiation. If, however, the irradiation of the spermatozoa be prolonged, the destructive action upon development is *not increased but rather diminished.* Hertwig regards the explanation of this apparent anomaly as due to the fact that, in the less strongly irradiated spermatozoa, true fertilisation does take place, but that the male chromatin is in such a disorganised condition that it itself acts as a " Contagium vivum " to the fertilised cell, and hence abnormal development occurs. On the other hand, if the spermatozoa have been subjected to long exposure to radium (say 12 hours), the male chromatin undergoes such complete damage that it takes no part at all in the subsequent cell-divisions; the spermatozoon here is regarded merely as a mechanical stimulus to parthenogenic development, in a manner analogous to the prick of a platinum needle by which Bataillon was enabled to induce parthenogenesis in frog's eggs.

G. Hertwig irradiated unfertilised frog ova and then impregnated

them with normal spermatozoa. He obtained results analogous to those obtained in the A series of O. Hertwig.

Subsequently to these investigations upon the action of radium upon development, O. Hertwig has produced very similar results by purely chemical agents. Normal unfertilised frogs' eggs were taken and fertilised with spermatozoa which had been treated with one of the reagents in question. Experiments were made with substances exhibiting various degrees of toxicity, but it soon became apparent that for success two conditions were essential:

(1) The reagent must not seriously interfere with the motility of the spermatozoa;

(2) It must not grossly alter the character of the protoplasm of the cells.

Three substances were found to be specially suitable for these experiments:

(1) A dilute solution of methylene blue.

(2) A 3 per cent. solution of chloral hydrate, with .25 per cent. of sodium chloride.

(3) A .25 per cent. solution of strychnine nitrate, with .25 per cent. of sodium chloride.

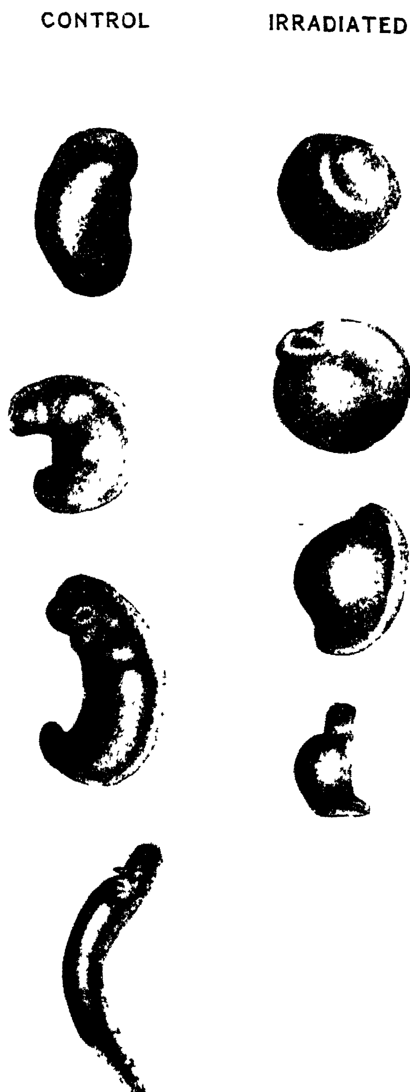


Fig. 17.—Triton Ova exposed to the beta and gamma rays from 5.3 mgs. of radium bromide for 5 minutes. The ova subsequently fertilised.

Restriction of development compared with non-irradiated ova for the same period, viz 9 days.

These reagents were employed for different times and

in different dilutions, and the net result of the experiments was that these chemical substances produced monstrous forms analogous to those resulting from irradiation by radium, as previously described. There is a further very interesting point in connection with this



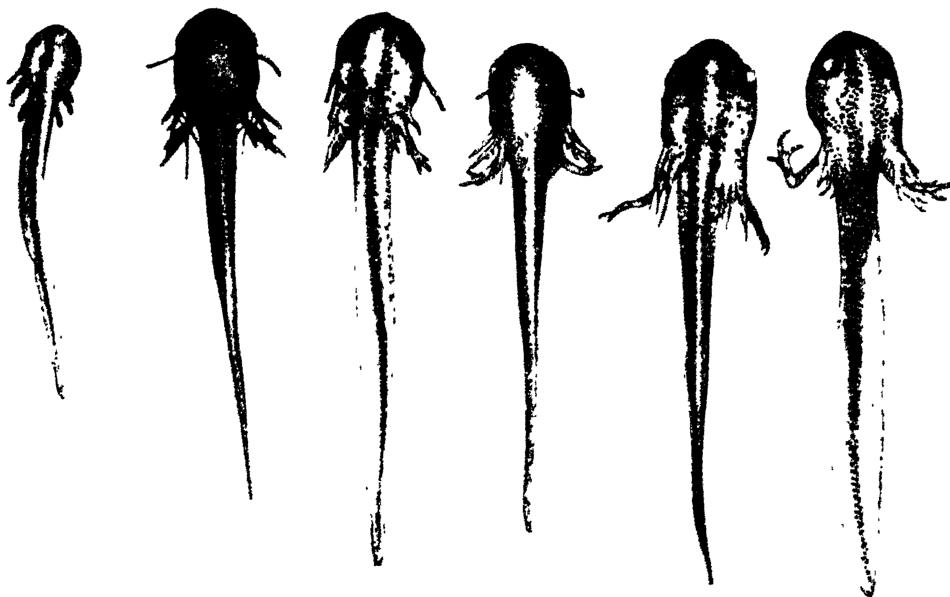


FIG. 18.—Triton Ova fertilised by spermatozoa which had previously been exposed to the beta and gamma rays from 50 mgs. radium bromide for 2 hours.
Restriction of development compared with Ova fertilised by non irradiated spermatozoa
Period of observation, 13–27 days.

series of observations: not only do the three reagents fulfil the conditions previously laid down of not unduly altering the motility and chemical composition of the spermatozoa, but they are each absolutely different in their chemical composition, and there seems no essential factor common to them to account for their action in this respect. This is of interest as indicating that the changes produced by irradiation, although perfectly definite, are by no means specific, since analogous results can be produced by diverse chemical agents, which again, in turn, do not seem to have any feature in common except their influence upon development.

O. Hertwig's observations of the retarding effects which the beta and gamma rays exert upon development extended to the ova of Triton. The ova were in some cases irradiated before fertilisation, in other cases they were fertilised by spermatozoa which had been previously irradiated. Development is in both cases hindered, as may be seen from Fig. 17 and Fig. 18 illustrating the two different experimental conditions.

Birds. The action of radium rays upon chick embryos has formed the subject of experiments by Tur, who published his results in 1904. He employed a series of eighty eggs in his researches; incubation was allowed to proceed for from 24 to 70 hours under the influence of radium. The amount of radium used is not stated, but the substance employed is described as a "radio-active preparation containing about 35 per cent. radium chloride, contained in a glass tube 33 millimetres long and 3 millimetres wide, placed upon the egg-shell, perpendicularly to its long axis, so that the embryo would be influenced by the radiations emitted from a surface of 100 square millimetres."

By such a procedure monstrous embryos were obtained, all presenting the same abnormal features. Generally speaking, the central parts of the embryos underwent the most profound alterations, the peripheral portions showing only insignificant modifications. Among the important central changes noted, the least severe was the complete absence of protovertebræ; this condition was only found in comparatively few cases, and in embryos otherwise normal which had been incubated for 45–48 hours. All the other embryos examined presented the features of developing shapeless monsters ("anidiens"). This type of monstrosity, which was obtained by 24–28 hours' incubation in the presence

of radium, consists of a blastoderm of normal diameter, but with an abnormally contracted transparent area, surrounded by thickened masses of vitelline entoderm. The primitive streak is only represented by its posterior part ; anteriorly in place of medullary plates, there is merely diffuse thickening of ectoderm, forming a plate with irregular outline. From this type partial development may proceed along one of two lines.

(1) After 45–48 hours the broad outlines of the central parts remain as above described. Around them appears a vascular area, with a well-marked terminal sinus; a blood plexus of ordinary appearance is formed, and gradually invades the central part of the blastoderm occupied by the rudimentary transparent area.

(2) In other cases (and these form the majority), the vascular area does not form at all. The peripheral growth of the blastoderm (after 50–70 hours' incubation) invades more than half of the yellow surface of the yolk, while the transparent area is reduced to a very narrow longitudinal cleft, varying in length from 1.5 to 3.5 mm., and in width never exceeding .02 mm., no traces of an embryo are discernible.

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X RAYS.

Some of the earliest systematic observations of the effects of X rays upon developing forms were made by Perthes. He exposed ova of *Ascaris megalocephala* for 1 hour, at 8–10 cms. distance from an X-ray bulb, the spark gap being 6.5 cms., and the total dose given 24 Holtzknecht units. The temperature was observed throughout the exposure and not allowed to rise above 25° C., the ova being covered with a thin vulcanite plate to eliminate any possible effects from warmth and light. After irradiation the ova were suspended as "hanging-drop" preparations over a suitable moist chamber. After 12 hours, control specimens had either completed division into the two-cell stage or signs of its commencement were visible: the irradiated specimens, on the other hand, exhibited no signs of division, and not until 24 hours after their exposure did the irradiated ova show some indication of division. After 36 hours, control ova had reached the four-cell stage, the irradiated being in the one- or two-cell phase; while when the controls were at the sixteen-cell phase the experimental ova had only reached the four-cell stage. Side by side with this retardation of development, irregularities in the mode of cell-division soon manifested themselves.

The general appearances of the irradiated ova fell into two divisions accordingly as they are more or less severely damaged by the exposure. In the first or more severely damaged class are those ova which were given a dose of over 24 Holzknecht units; these do not proceed to the formation of a recognisable embryo, but remain as a group of cells abnormally arranged and irregularly sized. Non-irradiated controls, examined at the same time, showed a well-developed embryo. The second group, or less severely damaged ova, contains those whose degree of irradiation did not exceed 20 Holzknecht units. These produced monstrous embryos, partially resembling normal forms, but presenting irregular cell masses; sometimes such a mass would occupy the position of the tail of the embryo—the head end being normal—and *vice-versa*; while in other cases the two ends appeared normal, and the irregular cell outgrowth was situated more or less in the middle.

Among the less intensely irradiated specimens some normal forms occurred among the monstrosities just described. It is

important to note, however, that whether the intensity of irradiation was of the higher or lower grade, the cells were not killed outright, they underwent division to a greater or less degree, even though the forms produced were atypical and of but low vitality.

If the ova were irradiated, after being allowed to undergo development to the sixteen-cell stage (third day), damaged forms still resulted, but the damage was not so great as when the irradiation had taken place prior to division.

Histological examination showed that the equatorial plates were first formed in the irradiated specimens after 24 hours, while in the controls they could be seen after 6 hours. The chromosomes also showed destruction.

The ova of *Ascaris megalocephala* are extremely sensitive to soft X rays, and Hastings has observed a retardation of their growth when they are exposed to the secondary X rays emitted from copper. Under his experimental conditions the intensity of these secondary rays was a few per cent. of that of the primary beam, and with an exposure of an hour or two he was able to detect a subsequent delay in the development of the ova when compared with their normal rate.

Insects. The first insect larvæ whose behaviour under the influence of X rays was observed, were ordinary silkworms. The experiments were carried out by Bordier, a daily dose of 7 to 8 Holzknecht units being administered. The main differences between the experimental and control animals were that the experimental showed (1) increased restlessness, (2) smaller size and (3) darker colour. Moreover, the spinning commenced five days later than in the controls, the resulting cocoon was only half the normal size and the moth did not emerge. On opening the cocoons, four out of six chrysalides were found to be dead, and the change from caterpillar to chrysalis was only observed in the posterior segments of the animal, while the front parts were all adherent to the cocoon as a result of a sanguineous exudate from the mouth. The two specimens which were yet found to be alive showed but a low degree of vitality and gradually dried up. Further experiments regarding the action of X rays upon caterpillars and pupæ were carried out by Hasebroeck, from which it will be seen that some species appear more sensitive than others to the action of the rays, and pupæ less sensitive than caterpillars. Thus, of six half-grown caterpillars of the foreign butterfly

Charaxes, which in four or five "sittings" received in all 117 minutes' irradiation, five died in the caterpillar stage, one formed a pupa which soon died and dried up.

Caterpillars of the "Small Tortoiseshell" butterfly (*Vanessa urticæ*) were more resistant. In all, the irradiation lasted 140 minutes, and the various "sittings" were continued up to the pupal stage. The resulting pupæ were smaller and darker than the controls; they developed into butterflies which emerged simultaneously with the normal specimens, and were, generally speaking, well developed. The power of flight was, however, entirely absent, and on measurement the span from wing-tip to wing-tip was found to be smaller than the normal (44 : 49). The pattern on the wings was indistinct and the colour darker than usual. These abnormalities of tint and pattern were found, on microscopic examination, to be due to an abnormal arrangement of the scales and to an excess of black pigment in them.

In a further experiment irradiation of the caterpillars of the "Peacock" butterfly (*Vanessa Io*) for a total period of 83 minutes did not hinder pupation nor the development of normal butterflies. Insects which had been allowed to undergo normal development as far as the pupa stage, and were then subjected to irradiation by the X rays, appeared uninjured by the exposure. Among the pupæ examined were those of the "Small Tortoiseshell" (*Vanessa urticæ*), of the "Red Admiral" (*Vanessa Atalanta*), which received total exposures varying in different cases from 30 to 185 minutes; of the "Peacock" butterfly (*Vanessa Io*), and of the "Spurge Hawk" moth (*Deilephila euphorbiæ*), which last example was irradiated in all for 218 minutes. No abnormalities were noted in any case in the mature insects.

An extensive series of observations has been made by Hastings, Beckton and Wedd as to the effect of X rays upon silkworms in the various stages of their development. The experiments were continued over a period from May, 1909, to September, 1911, thus comprising nearly three complete cycles of their life-history. The details as to the various methods by which the irradiation was carried out may be found in the original memoir, the most important features of the results obtained being as follows:

I. *Fertility of eggs*. In the case of X rays applied to the insects in the first generation, no definite result is obtained, though there

is an indication that the fertility of these insects is somewhat diminished. The immediate descendants of these insects, however, though not themselves receiving X rays, are markedly less fertile. If X rays be applied in two successive generations, the fertility of the second does not depart so greatly from the normal; but, nevertheless, appears to be diminished.

II. *Date of hatching out of eggs.* In every case in a series of thirteen sets of experiments, acceleration, as estimated by the total proportion of hatching out occurring before a given date, is indicated in the case of eggs themselves subjected to X-ray treatment or the offspring of X-rayed parents; this finding is confirmed by the results of a series of experiments made or completed during the following year. On the other hand, a retardation is indicated in the hatching out of the eggs of the second generation; while there is also some evidence that this retardation can be warded off by repetition of irradiation in the second generation.

III. *Weight of cocoons.* An extensive series of experiments indicates that X-ray treatment as above applied, in one generation only, stimulates larval growth, as estimated by weight of the cocoons. As might be expected, not every experiment shows increase in weight of resulting cocoons as compared with controls, since experimental error may in an individual case quite well mask the individual result; but on the whole the results show well-marked agreement. On the other hand, radium in the dosage employed has exerted a depressing effect as regards weight of cocoons, while there is also evidence that X-ray treatment, when repeated as above in a second generation, has a depressing influence on metabolism as judged by this criterion.

IV. *Large doses of radiations.* Both X rays and radium applied as above in large doses to larvæ exert injurious and even destructive effects; there is in this series of experiments no evidence whatever of stimulation.

Amphibia. In 1904 Gilman and Baetjer exposed the eggs of the curious amphibian *Amblystoma* to the X rays. The exposures were made for different periods, and the duration of each exposure was 15 minutes.

The first difference observed between the irradiated eggs and the controls was an acceleration of development for a short time (sometimes up to the tenth day) in the irradiated; it must,

however, be noted that although the development was accelerated, yet the forms produced were abnormal. About the tenth or eleventh day the controls had caught up with the irradiated samples, which then either remained the same size or assumed various grotesque shapes; the chief abnormalities observed consisting in roughening and wrinkling of the integument, the non-development of external gills on any of the specimens, and the ill development of the caudal membrane.

C. R. Bardeen in 1907 published the results of his experiments upon the fertilization of toad ova by irradiated spermatozoa. Toads were selected as being abundant and easy to obtain when sexually mature, while the spermatozoa retain their motility and power of fertilization for several hours when suspended in water. Pairs of toads were taken, the males separated from the females, and the latter washed for several hours in running water. From the testes and spermatic ducts of the males a thick suspension of spermatozoa was obtained; this was slightly diluted and divided into two parts, one being irradiated while the other served as control. The periods of irradiation varied from half an hour to two hours, a fairly hard tube was used and placed about four inches from the suspensions.

Several short strings of mature ova were placed in the control and various irradiated suspensions (after removal from exposure to the X rays), and allowed to remain for twenty minutes, after which they were removed and placed in large dishes of water and their subsequent development watched. All the ova fertilized by the control spermatozoa developed along normal lines, while those fertilized by the irradiated material showed greater or less degrees of abnormality.

It was observed that spermatozoa when removed from the body began to show a diminution in motility and fertilizing power in about half an hour; both motility and fertilizing power lasted much longer, however, in cool than in hot weather, and slightly longer in normal than in irradiated samples. On cool days they retained their fertilizing power for two hours.

When spermatozoa had been irradiated, and yet retained their fertilizing power, ova fertilized by them developed normally, or even showed slight acceleration at first, but beyond the gastrula stage, division was found to be retarded and at the time of hatching marked deformities were noticeable.

As regards external form the irradiated spermatozoa gave rise to larvæ with abnormally shaped heads, the cœlom was frequently distended, while the tail was short, deformed and dorsally flexed.

The changes in internal organs were most marked in the vascular system, which shewed but little development, the heart and great vessels being markedly affected. In the nervous system, the brain, and frequently also the spinal cord, shewed incomplete or abnormal development, irregular growth and failure of tissue differentiation being generally evident. The nerve cells exhibited pigmentary degeneration and the central canal was filled with disintegrated cells. In one specimen the hind-brain and anterior part of the cord shewed unilateral development.

As regards the organs of special sense, the eye presented the most marked abnormalities, the nose and ear being rudimentary rather than deformed. In the alimentary canal, the abnormalities were very variable, the mouth was patent in all cases, while the lips and jaws were rudimentary. Traces of internal gills were generally present, although, owing to non-development of the vascular system, these were rudimentary. The liver, pancreas, intestine and lungs were generally not well developed. The pro-nephric tubules frequently exhibited marked swellings, while distinct meta-nephric tubules were generally absent. Abnormalities were also noticed in the development of the musculature of the body, while the ectoderm generally shewed irregular outgrowths, and in one case marked downward ingrowths were present.

The cellular elements of the tissues generally presented clear outlines. In general these tadpoles shewed marked resemblances to the forms described by Schaper which had been themselves irradiated.

Subsequent investigations by Bardeen (1909) shewed that spermatozoa, ripe ova and freshly impregnated ova of the frog and toad were very susceptible to the X rays. This susceptibility was observed to be diminished in the second hour after fertilization, after which it rapidly increased to a maximum in the earlier stages of cleavage, while it was markedly diminished during the stage of gastrulation.

In 1911 the same observer published further extensive observations upon the subject, the exposures varying in duration from twelve minutes to two hours. While irradiation did not appear to

diminish the power of spermatozoa to effect fertilization, the following results were noticed as a result of fertilization with such irradiated spermatozoa.

(1) Development was stopped during cleavage.

(2) Gastrulation was abortive or abnormal. Spina-bifida forms and forms with an abnormally large anus being produced, while in some cases hemi-embryos resulted.

(3) Gastrulation was completed, though more or less abnormal, and no distinct larval differentiation occurred.

(4) The larvæ shewed marked abnormalities very early in development.

(5) Abnormalities appeared which became more marked with the approach of the time for hatching.

(6) After hatching, larvæ failed to grow into normal and healthy tadpoles.

(7) There was failure of normal metamorphosis.

Some of the ova fertilized by spermatozoa irradiated for one hour appeared abnormal during gastrulation, but most appeared abnormal during larval differentiation and before hatching. Few were differentiated into tadpoles capable of much development.

In ova exposed for one hour before fertilization the abnormalities appeared earlier than in normal ova fertilized by irradiated spermatozoa, but about the same number eventually reached the tadpole stage.

Eggs exposed during fertilization for forty-five minutes shewed many abnormal forms during the late cleavage stages and during gastrulation, while few underwent definite differentiation into larvæ. Of eggs exposed during the early cleavage stages for forty-five minutes only a few underwent gastrulation. Specimens irradiated for forty-five minutes in the early stages of gastrulation practically all developed normally. But if a second exposure of forty-five minutes were given many abnormal forms resulted and only a few became well-developed tadpoles.

In the case of young larvæ exposed for two hours, many became abnormal and died early; some, however, developed normally and underwent metamorphosis. Exposure of tadpoles for two

and a half hours soon after they begin to swim was usually followed by death within a month. Tadpoles exposed for two and a half hours during metamorphosis usually had the metamorphosis interrupted, while in some cases death ensued within a month.

The Tables on pp. 143, 144 contain some of Bardeen's most interesting results. Careful and detailed descriptions are given of the development of different organs as the result of irradiation at different periods of development.

Birds. The action of X rays upon the development of the chick was first observed by Gilman and Baetjer in 1904. The type of rays used by them was that corresponding to No. 6 Benoist, and the eggs were exposed for periods of about 6 minutes at a distance of about 15 cms. from the anode of the bulb. For 36 hours after exposure the experimental embryos showed an accelerated development over the controls; after that period they were retarded. A specimen examined on the fourth day showed deformity of the head and inhibited development of the eyes. In older specimens the limbs were distorted, projecting from the body in various eccentric ways, and in those cases where feathers had commenced to grow their distribution was noted as patchy.

Bordier and Galimard in 1905 did a further series of experiments upon chick embryos. The developing eggs were subjected to daily irradiations of 15 Holzknecht units, and after 20 days' treatment and simultaneous incubation at 40° C., no trace of an embryo was to be found. In specimens where development had been allowed to proceed normally to a certain stage, and which were then exposed to the X rays, growth was apparently arrested from the time when the rays were first applied.

Observations of a similar nature were made in 1911 by Gaskell, who found that exposure of the embryos to the rays caused a diminution in the mitotic activity; the extent of this was determined by counting the mitotic processes in parts of the forebrain of embryos which had received various degrees of exposure. He showed that the lowering of the rate of cell growth was not permanent and was completely recovered from, provided the irradiation had not exceeded a certain amount. His conclusion that "the greater the reproductive activity the larger is the X ray dose required to prevent further development" is not easy to reconcile with the frequently observed fact that rapidly growing cells are very sensitive to the rays.

TABLE 40

GIVING SUMMARY OF THE MORE SUCCESSFUL EXPERIMENTS MADE UPON THE ACTION OF X RAYS UPON SPERMATOZOA OF TOAD AND FROG. FIGURES IN BRACKETS INDICATE PERCENTAGE OF EGGS DISCARDED BECAUSE OF LACK OF FERTILIZATION.

(C. R. BARDEEN *Am J. Anat.* xi. 435. 1911.)

Designation of Experiment.	Animal.	Length of Exposure of Sperm.	Number of Ova Studied	Results										
				Gastrulation Incomplete					Gastrulation Complete					
				Not Fertilized	No Gastrulation	Protruding Yolk Mass	Hemi Larvæ.	Spinabifida	No Larval Differentiation.	Abortive Larvæ	Abnormal Larvæ	Defective Tadpoles	Normal Specimens	Remarks.
				Per cent.	Per cent	Per cent	Per cent.	Per cent	Per cent	Per cent	Per cent	Per cent.	Per cent	
1	Toad	15 m.	75	[49]	—	—	—	—	—	9.5	64.3	0.26	2	Experiment discontinued two weeks after irradiation; at this time 11.9 per cent. appeared normal.
2	Frog	30 m.	156	[2]	5.4	9.3	0.7	12.4	11.9	21.2	35	4	—	
3	Toad	37 m.	150	[50]	—	—	—	—	—	98.7	—	1.3	—	
4	Frog	30 m.	650	[0.8]	—	—	0.5	0.1	—	3.7	77.4	0.18	3	
5	Frog	2 hrs.	28	[50]	—	—	—	—	—	—	96.5	3.5	—	
6	Frog	20 m.	267	[3.5]	—	—	—	—	—	0.7	82.8	11.6	4.9	
7	Frog	12 m.	370	[25.3]	0.8	—	—	—	—	7.8	76	0.15	4	
8	Frog	40 m.	60	[66]	—	1.7	—	—	—	—	76	13.3	8.3	
9	Toad	70 m.	250	—	—	—	—	—	—	—	97.1	2.9	—	All appeared abnormal 5 days after fertilization.

TABLE 41.

TABLE GIVING SUMMARY OF EFFECTS OF EXPOSURE OF OVA BEFORE FERTILIZATION. FIGURES IN BRACKETS INDICATE PERCENTAGE OF EGGS DISCARDED BECAUSE OF LACK OF FERTILIZATION.

(C. R. BARDEEN *A. J. A.* 451.)

Designation of Experiment	Animal.	Length of Exposure of Ova.	Number of Eggs.	Results. Gastrulation Incomplete. Not Fertilized	No Gastrulation.	Protruding Yolk Plug	Hemi Larvæ.	Spinabifida.	Gastrulation Complete. No Larval Differentiation.	Abortive Larvæ.	Abnormal Larvæ.	Defective Tadpoles.	Normal Specimens	Remarks.
				Per cent	Per cent.	Per cent.	Per cent	Per cent	Per cent	Per cent.	Per cent	Per cent.	Per cent.	
1	Toad	12 m.	503	[0.06]	—	—	—	—	—	—	10.7	5	84.3	Control gave about same percentages
2	Toad	30 m.	703	[0.05]	—	—	—	—	—	50	9	14	35	Five specimens followed to metamorphosis.
3	Toad	45 m.	679	[0.44]	—	1	0.8	—	7.1	24.7	36.4	10.9	19	But one specimen could be preserved through metamorphosis.
4	Toad	$1\frac{1}{4}$ hrs.	216	[0 44]	—	3	1	—	5.59	26.8	31	1.4	4.2	Eggs slightly injured. X ray current weak.
5	Toad	$1\frac{3}{4}$ hrs.	428	[0.56]	—	3	—	—	3.7	38.3	40.2	12.4	5.1	Several specimens followed to metamorphosis.
6	Toad	1 hr.	846	[22.0]	—	5.7	1.3	17	2.7	35.6	34.9	2.3	0.4	X ray current stronger than in above experiment.
7	Frog	$1\frac{1}{4}$ hrs.	177	[1]	—	9	2.3	6.2	11.3	21.5	48	1.7	—	

Mammals. Numerous experimental researches upon the action of X rays on fœtal or young mammals have been made.

The effects of irradiation were, in all recorded cases, deleterious; whether the animals were exposed to the action of the rays before birth (by irradiating pregnant females), or whether newly born specimens were wholly or partially exposed.

Försterling obtained retardation of growth by giving 40-hour-old rabbits single exposures of from 5–20 minutes, the distance from the tube being 20–24 cms. Irradiation of a particular part of an animal led to a diminution of growth of that particular part. In some instances the head only was irradiated, with the result that not only the head of the experimental animal was smaller than normal, but the whole body suffered retardation of growth. Cohn irradiated the heads of pregnant doe-rabbits, the rest of the body being enclosed in a lead-lined box. The total duration of the various exposures was 3 hours, and the pregnancy continued to full term. For the first fourteen days after birth the young of the irradiated does resembled the young controls, but afterwards a very marked inhibition of growth occurred, and after seven weeks the experimental animals had only attained about one-third of the size of the controls. In addition to this puny development, other changes were noticeable, namely, a staring coat, blepharitis and keratitis.

Lengfellner exposed pregnant guinea-pigs three days before term, the times of irradiation being 20, 50 and 60 minutes respectively. The young were ascertained to be alive before the experiment, at the conclusion of which the throats of two of the parent animals were cut and the young immediately removed. They showed only slight degrees of vitality and died in 10 minutes; a third irradiated animal was allowed to survive, and after 5 hours gave birth to three dead young ones. Irradiation of a single limb (the hind leg of an eight-days-old puppy) produced inhibition of growth in the experimental limb, and seven and a half months later the shortening was as great as 8 cms. The exposure in this case was of 12 minutes' duration.

Newly-born dogs were irradiated by Krukenberg; one was treated on the fore-legs and the other on the pelvis. Initially nothing abnormal was observable in either beast, but after a fortnight the parts which had been submitted to the action of the rays became depilated; after two months had elapsed the hair

grew again, but was sprinkled with white. The animal whose pelvis had been exposed developed normally, but the other showed marked changes; it was unable to stand upon its fore-legs and showed nervous symptoms, such as tremors of the head and front legs; its movements were disorderly, showing by turns sudden starts forwards, backwards, or to one or other side. Excessive irritability was a marked feature, and when approached the animal growled and attempted to bite.

Gradually both the ataxia and the tremors became less frequent, but the development of the fore part of the body was very markedly retarded, and the power of vision was obviously defective. Ophthalmoscopic examination revealed complete atrophy of the papilla on the right side, and a partial atrophy on the left.

As regards the animal irradiated in the pelvic region, the noticeable features were the small development of the pelvis, the short back and hind legs, and the consequent apparently large head and fore-legs; the general appearance of the animal suggesting that of a hyena. The behaviour of this dog exhibited nothing abnormal.

Analogous experiments on goats were carried out with the same results.

Walter, in 1912, published the account of his experiments on rabbits, guinea-pigs, dogs and sheep, and again obtained various destructive results. His paper contains a résumé of the experimental work undertaken up to the time of its publication, and is furnished with a full bibliography. The foregoing abstracts of experimental work upon mammals are taken from his "*Sammelreferat,*" though, for purposes of convenience the references to the original papers are given.

Bagg in 1922, published some very interesting results of experiments upon the action of radium emanation on mammalian development. The animals used were rats, and the radium emanation was applied by two distinct methods.

In the first method an "active deposit" was obtained by exposing a known quantity of sodium chloride to a large amount of radium emanation, generally about 500 milli-curies. The salt with its active deposit was dissolved in sufficient water to give a "physiological saline solution." Pregnant rats were injected subcutaneously in the shoulder region and intravenously in the

caudal vein, the usual dose administered being from 3 to 4 minims. In consequence of the rapid loss of activity of such radio-active solutions, injection was made immediately after preparation of the solution.

Preliminary experiments showed that a dose of 5 milli-curies was the maximum applicable to the aims of the experiment.

The animals so inoculated form two series :—

(*a*) Subcutaneous injections after mating.

(*b*) Subcutaneous injections before mating.

(*c*) Intravenous injections after mating.

Series (*a*). *Subcutaneous injections after mating.* Sixty-five normal pregnant rats were treated at different periods (varying from seven to twenty-one days) after mating. Some of the animals were killed and examined ; others were allowed to go to term.

Various degrees of developmental disturbance in the embryos were noted as the result of the experiment.

(i) In many cases no embryonic development occurred, or the embryos were aborted or absorbed at an early period of their existence.

(ii.) In other cases embryos were killed by the treatment, but were removed and preserved before absorption could take place. These showed marked hæmorrhagic extravasations, notably in the subcutaneous tissues and in the meninges. Generally these hæmorrhages were found in the dorsal mid-line of the body. In one case a large hæmatoma in the subcutaneous tissue had exerted sufficient pressure upon the spinal cord as to produce dislocation. It was found that the fœtuses in any given litter showed marked variations among themselves in the degree to which they were affected.

(iii.) Several young of a single litter were born alive, and showed areas of hæmorrhage. Their mother died, and foster-mothers refused to nurse them.

(iv.) In some cases normal litters were produced. The offspring of these were observed for two generations, but exhibited no deviation from the normal.

Series (*b*). *Subcutaneous injections before mating.* Seventy-seven females were treated, and of these eleven died before mating as the result of the injection. The injections were made at periods varying from five to twenty days before mating. Only three

litters showed abnormal young, the most interesting case being a litter of seven in which pronounced hæmorrhages were found. Generally, however, the female was rendered sterile by the injection, or the embryos were killed and the products of conception absorbed. Seventeen females were killed at different intervals after mating: these showed hæmorrhagic or cystic ovaries and uterine congestion. Here irradiation had so profoundly modified the maternal structures that either fertilization did not occur, or if embryos were formed they died at a very early period and were almost completely absorbed. In these cases nodules were observed in the uterus, but it was impossible to differentiate histologically between maternal and embryonic elements.

In other cases both mothers and offspring appeared normal. Some of the young attained maturity, were mated and produced normal offspring.

In the second method X-ray radiation was allowed to act through the ventral abdominal wall of pregnant rats nearly at full term. Ten animals were exposed at the end of about nineteen days of pregnancy. It was found that exposure to about 1350 mc. hours of radium emanation was sufficient to produce marked changes in the embryos, and yet leave the mothers sufficiently uninjured to nurse their young until after the weaning period. On increasing the dose to 3378 mc. hours, the young were either killed outright or died two or three days after birth. In the animals treated for 1350 mc. hours the main points of interest are the following :—

(i.) The young were born two or three days after treatment alive and apparently normal.

(ii.) About ten days after treatment about half of each litter became markedly anæmic, showed profuse œdema and then died. There was a slow development of hæmorrhages into the spinal cord and meninges, with consequent compression of the nervous structures. The only other pathological conditions noted were in the liver and intestines. The liver cells showed fatty degeneration, while the epithelium of the intestinal mucosa exhibited disquamation.

(iii.) The other half of each litter survived the treatment, grew to a normal size, and survived for at least eighteen months. The first abnormality noticed was that the eyes became smaller than

normal, the pupils were opaque, there was more or less complete closure of the lids and total blindness. Histological examination showed that the retina was missing, and the choroid was represented only by a few pigment cells. The cornea was about three times as thick as normal, and was covered with three or four layers of opaque squamous epithelium. The optic nerve was very small and only about one-third of its normal size.

As regards the nervous system, these adult animals, which had been irradiated *in utero*, apart from their blindness behaved in a remarkably normal manner. There was no ataxia, no apparent impairment of hearing, and no evidence of abnormal cutaneous sensations. When, however, these animals were subjected to autopsy very marked changes were found in the central nervous system. The cerebral hemispheres showed great reduction in size, and in many cases the cortical substance was so reduced that but little remained. Those portions of the brain which were ontogenetically older (the archiostriatum and the cerebellum) were apparently normal. The optic tracts were markedly atrophic. Corresponding with these developmental defects of the central nervous system, the skull was asymmetrical, narrow, thicker than normal, and concave in the frontal region.

The testes were markedly atrophic, and the epididymis was represented only by a rudiment of the tail of the organ. Histologically there was but little evidence of spermatogenesis. In the case of the ovary, this organ was reduced to about a quarter of its normal size, and the Graafian follicles were entirely missing. The liver, kidney, spleen and other organs showed no histological abnormalities.

Histological examination of irradiated human fœtus in utero. Friedrich records the results of a histological examination of an irradiated human fœtus. The mother (æt. 33) was suffering from advanced tuberculosis, and it was found necessary to terminate the pregnancy. To this end the abdomen was subjected to the X rays; thirty-three sittings of 5 minutes each were given, without, however, producing the desired result, and operative measures were resorted to. The tissues of the fœtus so obtained were hardened in formalin, and stained by van Gieson, hæmatoxylin or hæmalum. As controls, the tissues of two fœtuses (of the same age as the experimental), which presented no pathological changes, were examined. In the irradiated specimens the

histological changes observed were few and almost exclusively confined to the spleen, lymphatic glands and leucocytes. The spleen presented the most marked changes, which consisted in (1) a marked diminution in the number of lymphocytes and of the cells of the spleen pulp; (2) pycnosis of the cell nuclei; (3) the appearance of finely or coarsely granular pigment of yellowish brown colour, which is apparently derived from the disintegration of lymphocytes or of red blood corpuscles; this granular debris was found in the liver and kidneys as well as in the spleen, but could not be demonstrated with certainty in the other organs examined; and (4) a very marked diminution of white blood corpuscles in all the blood vessels.

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CHAPTER IV

SEEDS, PLANTS, ETC.

RADIUM

MANY interesting observations have been made upon the effect of the various rays upon vegetable life, either upon seeds in various phases of their growth, upon leaves and budding twigs or upon the fully developed plant.

One is struck by the closely analogous effects caused by the rays to those which the animal kingdom provides. The same phenomena of modification and ultimate arrest of growth, nuclear changes of a degenerative character, with eventual destruction, follow upon exposure to large quantities of radium. The question whether the rays may exert a stimulating action upon cell life is apparently answered in the affirmative, especially by the experiments of Molisch which are described below. The observation may, however, be made with regard to these experiments that, although they do show that various twigs, if exposed to a certain intensity of radiation at a suitable stage of their development, bud earlier than similar twigs not submitted to the treatment, and thus appear to be stimulated, yet the action is upon a complicated organism, and is not traceable to a direct stimulating action of the rays upon a particular variety of cells.

Some of the earliest experiments were made by Dauphin in 1904, who showed that when a few milligrams of radium were kept near cultures of Mortierella for several days, a zone of inhibited growth appeared where the rays were most intense. He showed, by a careful study of the subsequent behaviour of the organism, that when the radium was removed and the spores placed under normal conditions they flourished again.

Matout, at about the same time, observed that prolonged

exposures (about a week) of the seeds of cress and white mustard to the beta and gamma rays from a few milligrams of radium hindered their proliferating power.

Koernicke showed that if the roots of beans and turnips were exposed to the beta and gamma rays from a few milligrams of radium for two or three days, their growth was brought to a standstill and then side shoots gradually began to form.

Some observations on similar lines by Mottram upon seedling beans have shown that with doses just short of what is required to completely stop the growth of the original root, its growth may be impaired for a certain time and then begin again. Not only so, but he has shown that if the same dose of irradiation be given to the root tips during the day and during the night, that much greater effects are obtained in those roots which were irradiated during the night. In view of the fact that growth of these roots is known to occur at night, this differential effect with the radium has been attributed by him to mean that cells in the process of division are more affected than other cells are by the same dose of irradiation, a similar result to that which he obtained with ova of *Ascaris megalocephala*.

Guilleminot made a prolonged study of the action of the beta and gamma rays upon the seeds of radishes and *poterium* in different phases of their activity. He has shown that the seeds are more affected by the rays when they are in an active phase than when in a latent phase of growth. Working with progressively reduced doses of irradiation, he obtained the minimum intensity required to produce a visible effect upon the seeds, with doses less than this he was not able to demonstrate any stimulation.

Further details of these interesting experiments cannot be gone into here, partly owing to the units in which the quantities are expressed.

Similar retarding effects upon the development of *Sinapis nigra, Panicum Germanicum, Papaver, Nicotiana* and *Amaranthus* were observed in a series of experiments by Congdon, who exposed them to the beta and gamma rays from 8 mgs. of radium. He found that these seeds were affected to varying extents when they were all exposed to the same quantity of irradiation. He was not, however, able to trace any relation between the sensitiveness to the rays and the chemical constitution of the seeds.

Falta and Schwartz exposed oats under growing conditions to radium emanation, and found that their growth was apparently accelerated, as may be seen from the following data:

(1) Concentration of emanation .0124 milli-curie per litre; after nine days:

In emanation vessel	45 shoots measured	18–19 cms. long.
,, ,,	21 ,, ,,	3–11 ,,
In control vessel -	20 ,, ,,	15–16 ,,
,, ,, -	28 ,, ,,	2–10 ,,

(2) Concentration of emanation .09 milli-curie per litre; after seven days:

In emanation vessel	96 shoots, total length	14 metres.
In control vessel -	94 ,, ,,	8 ,,

They state that the shoots were rich in chlorophyll, and in this

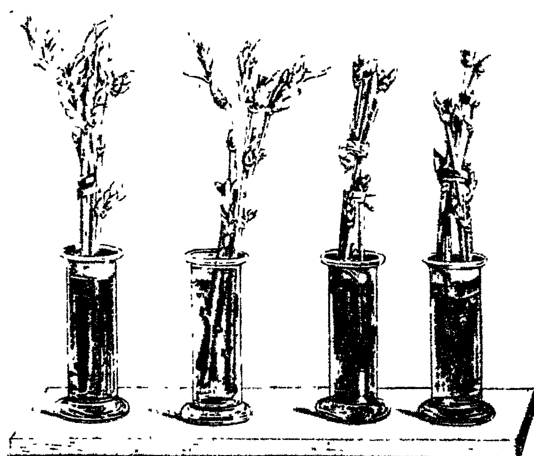


Fig. 19.—Syringa Vulgaris exposed to 29.4 mgs. radium chloride.

connection the experiments of Hebert and Kling (*vide infra*) upon lilac leaves are interesting, as showing that the chlorophyll-containing cell can exercise the power of assimilation when under the influence of nearly one hundred times the concentration of emanation used in the above experiments.

Some of the most important experiments upon plant life in this connection have been made by Molisch, who has shown that

if certain buds are suitably irradiated, then growth will be favoured or hindered thereby according as the buds are in the resting or growing stage respectively.

When buds of *Syringa vulgaris* were irradiated in the resting stage by beta rays, or when exposed to the emanation, the open buds appeared sooner than in the control experiments. The period at which the buds are irradiated is important, as the following series will show:

Experiment, 16th November. 24 hours' exposure of the buds

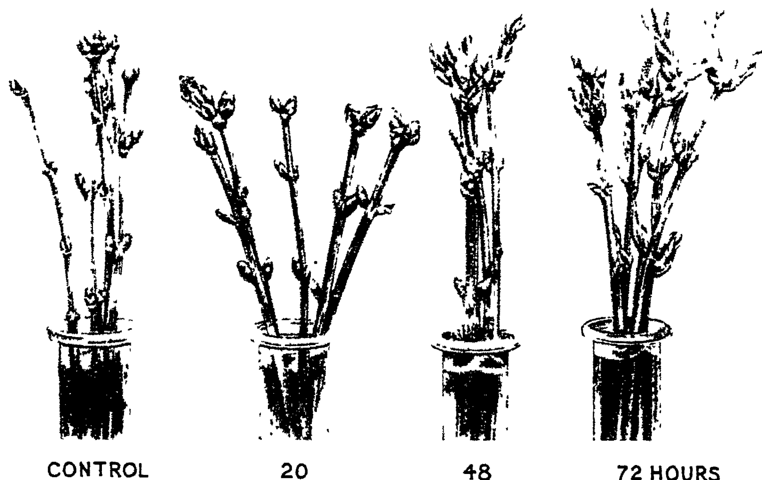


Fig. 20.—Syringa Vulgaris exposed to an atmosphere containing about .5 milli-curie per litre.

to 42.6 mgs. radium chloride. After thirty-five days no difference detected between the control and irradiated specimens.

Experiment, 21st December. 1, 24 and 48 hours' exposure to 29.4 mgs. radium chloride. Fig. 19 shows the result obtained on January 16th, and illustrates the favourable effect on the growth that the rays have had.

Experiment in January. 72 hours' exposure; not infrequently a retardation in growth is produced, the quiescent period is now over.

That the emanation has the same favourable influence may be seen from Fig. 20, which illustrates the result of an exposure of the buds to a concentration of about $3.6–7.2 \times 10^{-4}$ milli-curie per c.cm., the details being as follows:

Experiment, 27th November.

	No. 1 exposed to emanation for 20 hours.	
	,, 2 ,, ,, 48 ,,	
	,, 3 ,, ,, 72 ,,	
	,, 4 control.	
On December 10th,	,, 3 had budded. No others.	
,, 23rd	,, 3 copious budding.	
	,, 2 free budding.	
	,, 1 slight budding.	
	,, 4 control. No buds.	

Exposures made when the quiescent period was over showed that this concentration of emanation now acted as a deterrent to the growth.

Results of a similar nature were obtained with *Æsculus hippocastanum, Liriodendron tulipifera, Acer platanoides* and *Haphylea pinnata.*

As Molisch remarks, these results are of great interest as showing that under certain specified conditions buds may, under the action of the rays, be forced in an analogous manner to the ordinary methods employed, *e.g.* the hot-house.

It will be observed that the concentrations under which Falta and Schwartz observed accelerating effects were very nearly the same as were employed by Molisch.

A detailed study of the effect of submitting growing lentils, peas and wheat to measured doses of the emanation has been made by Stoklasa and Zdobnicky. They used the natural radioactive waters of Brambach and Franzensbad in various strengths and methods of application. Under these circumstances they found that if these plants were allowed to grow in an atmosphere containing the emanation, or in soil which was impregnated with it, then, provided the concentration did not exceed a certain value, a stimulating effect upon growth was caused; with increasing concentrations, however, harmful effects became manifest.

As an example of this effect may be cited these authors' observations upon *Polygonum fagopyrum,* which, when allowed to grow for fifty-two days in a nutrient solution which was renewed every five days, showed the following contrast with the controls:

Controls. Weight of 100 dried plants	9.45 grams.
(*a*) Exposed to 30 Mache units per litre	13.54 ,,
(*b*) ,, 60 ,, ,,	19.54 ,,
(*c*) ,, 600 ,, ,,	Growth interfered with.

These authors state that, as a result of making the soil radioactive, the growth of various plants is augmented, as seen from an earlier flowering and a greater yield of fruit. This stimulating effect upon growth ceases when the concentration reaches that of 300 Mache units per 5.7 kilograms of soil.

Hebert and Kling made experiments upon lilac leaves to see what effect an emanation-laden atmosphere would have upon their metabolism. They exposed the leaves in vessels of 30–35 c.cms. capacity, to the emanation from about .5 mg. of radium bromide, and came to the conclusion that chlorophyll cannot exercise the function of assimilation under the influence of the emanation apart from sunlight, at any rate, if this effect exists, it is sufficiently weak to be overcome by the opposite phenomenon of respiration. The vegetable cells appear, however, to be slightly altered by such exposures, for in studying the subsequent respiration and assimilation under solar action, they noticed a diminution in these functions with leaves that had previously been exposed to the emanation.

Fabre has made a study of the relative sensibility of various plants to radium emanation, and also of the microscopic changes consequent upon exposure to doses previously found to have deterrent or destructive effects upon them. The relative sensitiveness of *Sterigmatocystes nigra, Mucor mucedo* and *Linum calthartrium* was found to vary widely, the first-named was delayed in growth when the concentration reached 500 micro-curies per litre, the second for a concentration of .5 micro-curie per litre, and the last-named at 40 micro-curies per litre.

Fabre cites the case of a flowering lily which was irradiated with doses sufficiently strong to completely arrest development. Microscopical examination showed that the pollen grains contained only one or sometimes two incomplete nuclei, and that the atrophied condition had extended not only to the embryonic sacs, but to the entire ovules.

Lopriori exposed *Vallisneria spiralis* to the X rays for half an hour, and observed that the rate of intra-cellular circulation of the protoplasm was accelerated, while with the cessation of the radiation it returned to the normal. With an exposure of 1 hour, however, a permanent destructive effect was obtained, the protoplasm acquired a yellow colour and became granular and coarsely vacuolated; with a 2 hours' irradiation the protoplasmic move-

ment did not cease, but the chlorophyll granules began to lose their colour.

The same author also observed an inhibitory effect of X rays upon the development of pollen tubes on *Genista* and *Darlingtonia*, although the development was resumed after the conclusion of the experiment, during which the pollen grains had absorbed a considerable quantity of water.

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CHAPTER V

BACTERIA

RADIUM.

THE first recorded attempts at finding the effect of the rays from radio-active substances upon bacteria are those of Pacinotti and Porcelli in 1899.

They used preparations of uranium powder, and after exposures of numerous varieties of bacteria (including proteus, cholera, tubercle, diphtheria and typhoid) to these preparations for periods up to 24 hours, they state that the organisms were killed.

In view of the intensity of irradiation which subsequent work has shown to be necessary for a lethal effect upon such organisms, it is difficult to believe that the effects they describe were in reality due to the rays from the uranium. Freund, in 1903, was not able to substantiate their results.

Among the early observations on this subject with radium were those made by Strebel. Growths of *B. prodigiosus* upon agar-agar were exposed by him to the rays from a quantity estimated at 20 mgs. of radium under various conditions of screening; after the rays had been acting upon the organisms, their degree of growth was compared with that of non-irradiated specimens of the same organism. In general, the growths were hindered after exposure to the rays.

These observations of Strebel received confirmation and extension by the experiments of Aschkinass and Caspari in 1901, who worked with the same organism, and were able to show that the greatest effects were caused by the alpha rays.

Pfeiffer and Friedberger, who used a pure preparation of 25 mgs. of radium bromide, investigated the effects of the rays

upon typhoid and cholera bacilli. When such bacterial growths upon gelatine were held about 1 cm. above the capsule no growth was obtained within a certain zone of irradiation after exposures of 48 and 16 hours respectively. Anthrax spores, which are very resistant to bactericidal agencies, appeared to be more resistant, 72 hours' exposure being necessary for their destruction.

Hoffmann found similar effects with *B. prodigiosus, Staphylococcus pyogenes aureus* and *Anthrax*, and his investigations showed that the easily absorbed rays from radium were the most effective in preventing the subsequent growth of the bacilli.

Bactericidal effects due to the beta rays were, however, shown by Green upon a large number of micro-organisms, the concentration used being 10 mgs. of radium bromide concentrated over a surface of about .7 sq. cm., also by Dixon and Wigham, who used a preparation of 5 mgs. of radium bromide under conditions such that no alpha rays were effective. The organisms *Bac. pyocyaneus, Prodigiosus, B. anthracis* and *B. typhosus*, after exposures of several days, did not grow upon the media situated just below the tube containing the radium salt. These authors did control experiments, as did Pfeiffer and Friedberger, to show that the inhibitory effect upon the bacterial growth was not due to any action of the rays upon the medium.

Strassmann, in 1904, made a comparative study upon a large number of organisms, and found the time of exposure to 10 mgs. of radium bromide necessary for a lethal effect upon them. Table 37 gives the main results of this enquiry. The thickness of mica and glass used are not available.

TABLE 42.

Organism.	Time for lethal effect.	
	Rays through mica	Rays through mica and glass.
B. prodigiosus -	24 hours.	36 hours.
Streptococcus -	24 ,,	36 ,,
Staphylococcus -	48 ,,	60 ,,
B. tuberculosis -	108 ,,	108 ,,

An alternative method of exposing bacteria to the rays from radium is to use the emanation that is evolved from it.

Some early observations of Danysz showed that anthrax bacilli, when exposed for a sufficient time to the emanation, did not grow. The same effects were shown later by Goldberg and Omeliansky in the case of typhoid, *B. coli* and certain luminous bacteria.

Dorn, Baumann and Valentiner made a number of observations upon the effects of the emanation upon typhoid, cholera and diphtheria bacilli. Prolonged exposure in all cases resulted in the death of the organisms. They observed that when a culture was growing throughout a volume of gelatine, only the organisms within 2 mms. from the surface were effected by the rays. The effects at this depth were almost certainly due to beta rays, the experiment at the same time illustrating the very slight extent of diffusion of the emanation through gelatine.

Bouchard and Balthazard studied the effect of comparatively small quantities of the emanation in modifying the chromogenic power and virulence of certain bacilli. They showed that in the case of *B. pyocyaneus* the first effect of exposure to the emanation is an interference with its secretion of pigment, further exposure leads to a reduction in the virulence of the organisms, and finally their reproductive power fails. They were able to show that degenerative features, such as elongation and curvature of the organism, were produced in these bacilli, analogous to those produced by antiseptics.

The experiments which have hitherto been described indicate that the alpha and beta rays from radium are capable of arresting and, if of sufficient intensity, of stopping the growth of cultures of various bacilli. It is difficult from the general trend of these experiments to state the amount of radiation required to produce a lethal effect upon a particular organism.

If it could be stated that a growth of some particular organism, when exposed, for example, to the beta rays from a definite intensity of radium per sq. cm. for a known time would be prevented from growing, such quantitative information would be of use in deciding whether the bactericidal action of such rays could be made of any clinical use.

Quantitative experiments have been made by later observers, who naturally have not had to contend with the difficulties which the earlier workers met with, especially in connection with the measurements of the quantities of radium, or of radium emanation dealt with.

Jansen, in 1910, investigated the effect of radium emanation in various strengths upon *B. prodigiosus* when growing upon agar-agar. He found that an exposure of such growths for 48 hours to .003 milli-curie was sufficient to sterilise them.*

All of the experiments so far described have been made upon various organisms when growing upon media.

Some experiments were undertaken by Chambers and Russ, who eliminated this factor by using emulsions of the organisms in distilled water. Any possible effect of the rays upon the medium is thus avoided, and quantitative data are more easily obtained than under the previous conditions. Such emulsions of *Staphylococcus pyogenes aureus, Bacillus coli communis, Bacillus*

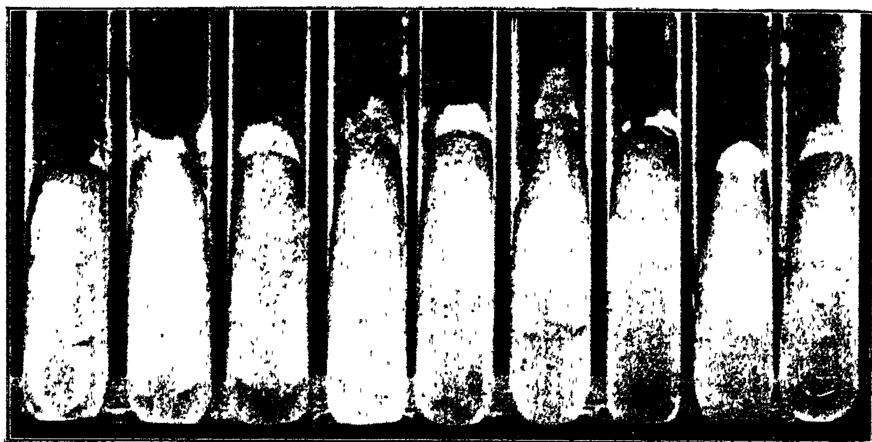


FIG. 21.—Action of beta rays on *Staphylococcus pyogenes aureus.*

pyocyaneus, B. anthracis and *B. tuberculosis* were exposed either to a measured concentration of radium emanation or a known intensity of beta rays.

At various times a known volume was removed from the influence of the emanation and planted upon agar-agar. The gradual bactericidal effect upon these organisms is illustrated in Fig. 21, which shows the effect that beta rays from 7 mgms. of radium bromide have upon the organism *Staphylococcus pyogenes aureus.*

The following table gives the time required for a sterilising effect, all the observations being reduced to one concentration, viz.

* His measurements of the quantity of emanation have been converted from Mache units to milli-curie for purposes of comparison

.5 milli-curie per c.cm. It appears to be justifiable to do this for purposes of comparison, for during the progress of the work it was shown that the destruction of the organisms (in this case *Staphylococcus pyogenes aureus*) occurred at an exponential rate.

TABLE 43 SHOWING TIME REQUIRED FOR STERILISING EFFECT PRODUCED BY .5 MILLI-CURIE PER C.CM.

Organism.	Time	
B. coli communis -	1 hour 5 min.	The number of organisms in the suspension was approximately one million per c.cm.
Staph. aureus - -	2 hours 0 ,,	
B. pyocyaneus - -	3 ,, 10 ,,	
B. anthracis - -	3 ,, 20 ,,	
B. tuberculosis - -	4 ,, 0 ,,	

It is possible to make certain comparisons between the various results of investigators.

Strassmann found that the periods for a lethal effect upon *Staph. pyogenes aureus* and tubercle bacilli were 48 and 108 hours respectively, a ratio of 1 : 2½; the ratio was 1 : 2 in the series of Chambers and Russ. Jansen found that the lethal point for *B. prodigiosus* was obtained by an exposure to .003 milli-curie per c.cm. for 48 hours (equivalent to .15 milli-curie for 1 hour). This organism was found to be twice as easily killed as *Staph. pyogenes aureus.* Calculations upon the data given by Green (*loc. cit.*) show that *B. coli communis* was 2.6 times as sensitive to the beta rays as *Staph. pyogenes aureus.* Chambers and Russ found the ratio 2 : 1.

An observation by these observers upon the agglutination of bacteria is possibly of some significance in indicating that quite different biological effects may be obtained by the alpha and the beta rays. It was observed that when emulsions of bacteria were exposed to the emanation (the alpha and beta rays being effective) marked agglutination occurred before the lethal point was reached. When exposures were made so that the alpha rays were cut out by a screen there was no agglutination, although a lethal condition was realised. The agglutination may have been dependent upon the alpha rays in an analogous manner to the coagulation of globulin first observed by Hardy (p. 98).

It has been shown that the emanation has considerable bactericidal properties when at a concentration of about .5 millicurie per c.cm. From a clinical standpoint this is a very strong dose. It would seem that the most likely cases in which the bactericidal properties of the alpha and beta rays might be made use of clinically would be in strictly localised conditions. This could be done by the injection of some fluid holding the emanation in solution; the choice of fluid is important, as there is a very wide range in the extent to which the emanation goes into solution in different fluids. Unfortunately most of the fluids having high coefficients of absorption cannot be used for purposes of injection into the body. Petroleum (liquid paraffin) is an exception, it has a coefficient of absorption of 9.55 at 20° C., and by virtue of its high viscosity is likely to remain longer at the site of injection than, for instance, physiological saline, which is not very viscous, and has a coefficient of absorption less than .3 at this temperature. The coefficient is a measure of the extent to which the emanation is dissolved by the fluid (p. 74).

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X RAYS

A considerable amount of work has been done upon the effects of X rays upon bacteria, but the results obtained by different observers have been by no means concordant. It is essential in this connection to discriminate between two different classes of experiment. In one class cultures or suspensions of bacteria were irradiated, while in the other injections of bacteria were made into living animals or plants, and the site of injection was submitted to irradiation.

The first kind of experiment is designed to show what may be called the direct action of the rays upon micro-organisms, the second the effect which X rays have upon their proliferation in a highly complex medium, which may itself react to the radiation. It is not surprising that quite different results are obtained under these conditions.

At the outset it may be stated that most of the common pathogenic forms appear highly resistant to the direct action of X rays. Suspensions of the micro-organisms in distilled water can be given an exposure to X rays many times greater that would cause a profound effect upon the skin, without inhibiting their subsequent growth. On the other hand it frequently happens in clinical practice that an ulcerated surface or glands, the seat of bacterial infection, when given moderate doses of X rays, shows a beneficial reaction, indicating that the growth of the bacteria has been hindered or even completely arrested.

The first experiments seem to have been those of Minck, who exposed typhoid bacilli in agar or gelatin culture for from 2 to 8 hours; a thin plate of vulcanite was interposed to cut off any light rays. The findings were negative.

Beck and Schultz experimented with chromogenic bacteria upon agar plates, and obtained no alteration either in growth or in chromogenic power. The spark-gap used was 12 cm., the distance from the anticathode 25 cm., while the duration of exposure varied from 20 minutes to 2½ hours.

Berton exposed broth cultures of *B. diphtheriæ* for 16, 32 and 64 hours. Subcultures were made, and two guinea-pigs were injected in each case. No difference was noted as the result of the irradiations in the growth or virulence of the organisms.

Sabrayès and Rivière experimented with plates of *B. prodigiosus* placed 15 cm. from the X-ray tube and protected with black paper from any possible light effects. Daily exposures, each of one hour's duration, were given over a period of 20 days. No differences either in chromogenic power, growth, or morphological characters of the organisms were observed.

In the foregoing experiments it will be observed that cultures of the organisms either on gelatin or agar, or in both, were exposed to the rays; in the following, animals were injected and then irradiated.

Lortet and Genoud injected eight guinea-pigs of the same age and weight with an emulsion of the spleen of a tuberculous guinea-pig. After two days three of the animals were subjected to the action of the rays at the site of injection. This exposure was continued for two months, the duration of each irradiation being at least one hour. At the expiration of the two months the five control animals showed no signs of tuberculous infection, while the experimental guinea-pigs showed swellings at the site of injection, with abundant secretion of pus and involvement of the lymphatic glands.

Fiorentini and Linaschi gave intraperitoneal injections of virulent cultures of *B. tuberculosis* to a series of guinea-pigs. Some of these served as controls, while others were irradiated. All the animals were found to be tuberculous, but the degree of infection was less in the irradiated than in the control animals.

Rieder, in 1898, published the results of his experiments upon bacterial cultures, and recorded inhibitory or lethal effects. Working in conjunction with Rosenthal and Buchner, he used a "Voltohm" apparatus with a coil of 30 cm. spark-gap, and the cultures were exposed in Petri dishes (the lids being removed) covered with lead screens in which a central aperture was cut. Exposures were made for about one hour, when the plates were transferred to the incubator and the condition of colonies observed. The organisms used were *Vibrio choleræ Asiaticæ*, *B. coli communis*, *Staphylococcus pyogenes aureus*, *Streptococcus pyogenes*, *B. diphtheriæ*, *B. Typhosus*. After varying periods of incubation, according to the organism under investigation, it was found either that growth was completely absent or the colonies were few and small in the areas which had been exposed to the rays.

A further series of experiments was undertaken to determine the action of the rays upon fully developed colonies of cholera vibrios, *B. coli* and tubercle bacilli. Inhibitory effects were obtained, but the organisms were not completely killed off in the irradiated areas. Observations confirming those of Rieder were made by Holzknecht and Spieler.

Further contributions to the subject were made by Ghilarducci, who obtained sclerosis and induration of the peritoneal and inguinal glands of tuberculous guinea-pigs. The same observer claims also to have destroyed anthrax bacilli by irradiating them in the presence of colloidal silver, and attributes his results to the effect of secondary radiations from the silver. Similar effects were obtained by the action of secondary radiations upon cultures of *B. prodigiosus* and *B. pyocyaneus*, and in this case the metal giving off the secondary rays was employed not as a colloidal solution in contact with the culture medium, but as "leaf" or powder whence the secondary radiations were allowed to reach the cultures. He concluded from his experiments that the lethal action was more marked the higher the atomic weight of the metal employed.

Good clinical results were reported by this author in the treatment of lupus, use being made by him of the secondary radiation emitted by silver and lead.

Certain experiments upon plants by I. and M. Levin should probably be considered in this connection. Many plants are subject to a tumour known as "Crown gall," this is due to a parasite—*Bacterium tumefaciens*—and it can also be produced by inoculation of an agar culture of the organism. The object of the experiments was to determine the effect of X rays upon the formation of Crown galls. A series of *Ricinus* plants was taken and inoculated with the micro-organism, immediately afterwards the site of inoculation was subjected to X rays, and X-ray treatment was given to each plant six times in the course of two weeks at intervals of two days. At the end of four weeks the irradiated plants showed no sign of Crown gall formation, while in non-irradiated inoculated plants large tumours had developed.

Murphy and Ellis found that the resistance of guinea-pigs to infection with tubercle bacilli was decreased by previous exposure of the animals to doses of X rays. They attributed this effect to the action of the rays upon the lymphocyte-forming tissues.

Experiments of a similar character upon mice by Browning, Gulbransen and Russ showed that with doses of X rays, which were sufficient to cause a loss of weight in the mice, there was no appreciable change in their susceptibility towards intraperitoneal inoculations of either virulent pneumococci or tubercle bacilli.

These observations do not necessarily contradict those of Murphy and Ellis, as the animals were different in the two cases.

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CHAPTER VI

SKIN

RADIUM.

THE first observers to direct attention to the fact that the rays emitted by radium are capable of affecting the skin were Walkhoff and Giesel. Both of them have recorded effects similar to those produced by X rays, namely, local inflammation followed by necrosis and ulceration. They further communicated the fact that such ulcers are very slow in healing, and that when healing has occurred a smooth pigmented scar remains. Becquerel, Curie and Aschkinass made experiments upon themselves and confirmed the inflammatory character of the phenomena produced by exposure of the skin to the rays from radium.

Systematic experiments upon the histological appearances of the skin at different times after irradiation have been carried out upon animals by Halkin, Thies, Dominici and Guyot. Each of these observers used a different type of animal, gave different periods of exposure and employed a different amount of radium. Strictly comparable results under such conditions are manifestly impossible, and the experiments will accordingly be given, in each case, in detail. Broadly speaking, the effects produced were inflammatory in character, the degree of inflammation depending upon the amount of radium used and upon the length of exposure. Among the earliest changes were dilatation and engorgement of the small vessels of the papillary part of the corium, followed by degeneration and irregular proliferation of the vascular endothelium. Infiltration by leucocytes was also an early feature, together with degenerative changes in the deepest layers of the epidermis. In those cases where the irradiation has been of

TABLE 44.

	Halkin.	Thies.	Dominici.	Guyot
ANIMAL USED	Pigs.	Guinea-pigs; skin shaved.	Guinea-pigs.	Mice.
METHOD OF APPLICATION	Radium capsule fixed by adhesive plaster.	Radium capsule fixed by adhesive plaster.	Radium capsule applied directly to the skin.	Placed in small boxes, irradiated from aperture in lid. Capsule face 1.5–2 cms. away from skin.
RA. PREPARATION	130 milligrams radium barium bromide.	20 milligrams radium bromide.	6 milligrams radium sulphate.	100 milligrams radium bromide.
COVERING OF CAPSULE	0.1 mm. aluminium.	"Mica."	Thin varnish covering.	"Thin mica."
DURATION OF EXPOSURE	2 hours.	6 hours.	5 minutes for 10 consecutive days.	48 hours.
RESULT	On the 8th day after exposure, the first sign appeared as a livid spot disappearing under pressure. The maximum change seen between the 20th and 24th days; irradiated area had a bluish livid tint, with a central scab, covering a small ulcer. Subsequent changes reparative. On 38th day only a slightly pigmented rather diffuse mark remained, healing complete.	On 2nd day, yellow pigmented area. On 5th, a raised dry brown scab; this disappeared by 14th day, leaving part dry and devoid of secretion.	10 days after commencement of exposure the skin became red; towards the third week an ulcer was formed, which was covered with a scab, which fell off between the 5th and 6th weeks, leaving a white supple scar, devoid of hair.	On 8th day, commencing desquamation. Between 15th to 20th days desquamation and falling out of hair marked. Surface reddened, serous exudation, which dried to form scab. From 30th to 40th days severe ulceration From the 12th week onwards slow healing.

sufficient duration and intensity, the picture is one of ulceration, the epidermis being completely destroyed and the corium exposed. Changes in the root-sheaths and hair bulbs appear early; they may at first be hypertrophic in character, as, for instance, in the root-sheath; but degenerative changes and falling out of the hair soon occur, a process which is accelerated by the invasion of the root-sheath by leucocytes. Degenerative changes and sometimes complete destruction also occur in the sebaceous and sweat glands.

A brief indication of the experimental conditions adopted by Halkin, Thies, Dominici and Guyot is given in Table 44 on p. 165.

The earliest experimental series was that of Halkin (1903). In a few of the earlier cases he used rabbits, but soon discarded them as unsuitable on account of the thinness of the epidermis, the excessive number of hair follicles, and the proneness of these animals to impetiginous lesions. In the series to be now described young pigs were employed, as the skin of these animals in many respects closely resembles that of the human subject.

The radium preparation was .13 gramme of radium barium bromide, enclosed in a suitable metal capsule and covered with a sheet of aluminium .1 mm. in thickness, this was fastened to the skin of the animals by adhesive plaster. Exposures were made daily in different parts, so as to obtain a series of irradiated areas which could be examined at various periods after the application of radium. On one side of the animal the duration of each exposure was 2 hours, while on the other side the time was restricted to 1 hour.

In the case of areas irradiated for 2 hours, the first macroscopic indication of change appeared about the eighth day, as a livid, somewhat diffuse spot, disappearing upon pressure; subsequently the periphery was much more markedly circumscribed. The maximum degree of change was noted from the twenty-second to the twenty-fourth days.

About this period the general surface of the irradiated area had a bluish livid tint, with areas of yellowish pigmentation and numerous scales of desquamated epidermis. Centrally there was a focus of more marked inflammation covered with a small dried scab, beneath which the surface of the skin was ulcerated. Subsequently the changes were more obviously reparative in char-



PLATE III.

CHRONIC HYPERTROPHIC RADIO-DERMATITIS, IN A CASE OF HUMAN CANCER OF THE THYROID GLAND, TREATED DURING SEVERAL MONTHS BY X-RAYS (*Dominici, Hæmatein Eosin Aurantia, 100 diameters.*)

acter; from the twenty-seventh to the thirty-third days changes were still visible, but gradually fading, while on the thirty-eighth day all that remained was a slightly pigmented diffuse mark with some local desquamation.

As regards the series in which exposures had been made for only 1 hour, it is sufficient to say that the reaction was later in appearing (fifteen days), was of less intensity and disappeared sooner than in the two-hour series.

Normal histological appearance of pig's skin. As regards the epidermis, the deepest layers of cells have a palisade-like arrangement, the interpapillary processes (as well as the papillæ themselves) are broad, and a few of the deeper epidermal cells contain pigment.

The corium consists of a dense connective tissue in which blood vessels are visible as dark streaks. Lying among the connective tissue cells are a large number of " Mast " cells; pigmented cells are relatively few. The lumina of the capillaries of the papillæ are exceedingly narrow; hair follicles are comparatively few and extend down deeply into the connective tissue. The subcutaneous tissue shows abundance of fat cells and numerous large arteries.

Histological examination of series irradiated for 2 hours. Areas of skin were removed at the expiration of different intervals after irradiation, the findings were as recorded below.

1 *day.* No change.

3 *days.* Dilatation of the capillaries of the papillæ and of the upper part of the corium.

5 *days.* Capillary dilatation more marked, but there is no change in the capillary walls and no perivascular infiltration.

7 *days.* There is a slight perivascular infiltration of leucocytes. The capillaries and small blood vessels are dilated and engorged; the endothelial cells have become swollen and their nuclei abnormally large. No infiltration in the corium.

In the foregoing cases no changes are visible in the epidermis, with the sole exception that in the seven days' specimen a few of the cells of the deepest or palisade-like layer show a tendency to the formation of small vacuoles and consequent slight displacement of the nuclei. The layer is, however, quite intact, and the cells of the rete Malpighii stain normally.

12 *days.* The capillaries of the cutis are greatly engorged, their endothelial cells highly vacuolated and their walls irregular, but

the degree of perivascular infiltration is still small. The small arteries and veins now begin to show degeneration. The central portion of the irradiated area shows the most marked changes ; in this situation cell-vacuolation appears in the corium, and cell débris are noted in the same situation. The connective tissue is considerably infiltrated with leucocytes, and there is an excess of pigment cells. In the epidermis the deep palisade-like layer shows a marked degree of vacuolation and stains badly.

14–15 *days.* Degenerative changes as above, but more marked.

18–22 *days.* In these specimens the central parts show various stages of ulcer formation. The horny epidermis is raised up and puckered by the exudate. The rete Malpighii has practically disappeared, being only represented by one or two layers of badly staining cells. The deepest (palisade) layer of the epidermis shows complete disorganisation, and only consists of an irregular mass of swollen vacuolated cells and cell débris. There is now considerable pigmentation, and pigment granules are also scattered between the cells and cell débris. Towards the free surface large spaces occur which are infiltrated with leucocytes, very likely as a result of bacterial infection. In the corium the vascular changes are still more pronounced and in the subcutaneous tissue the coats of the arteries show the changes characteristic of irradiation.

38 *days.* Here the changes have undergone retrogression. There is marked desquamation and some isolated cellular vacuolation. The leucocyte infiltration in the corium has, however, gone, and the vascular endothelium become normal.

A further extensive series of animal experiments upon the action of radium on the skin was carried out by Thies in 1905. He employed the same 20 mgr. capsule of radium bromide as in his other experiments. No special physical measurement was made of its activity, but its strength was such that a half-hour's irradiation of the human skin produced a definite reaction of the first degree with loss of epidermis, while irradiation of a flat angioma for 1 hour caused its ultimate disappearance. The animals employed by him in this research were guinea-pigs, the capsule being applied to the closely shaven skin by means of adhesive plaster. The duration of the exposure was in all cases 6 hours, portions of skin being histologically examined at varying periods after irradiation. The experimental findings are as detailed below,

and the times indicated refer to the period elapsing between the irradiation and the observation of its effects.

1 *hour*. *Macroscopically*. Appearance normal.

Microscopically. There is no change in the epithelial cells themselves, but here and there between the cells forming the deepest or palisade-like layer are some few leucocytes, and a few eosinophile cells have strayed close up to the stratum corneum which is, however, itself unaltered. A certain number of eosinophile cells have intruded between the cells of the root-sheaths of the hairs.

In the corium the most marked feature is a remarkable increase in the, ordinarily small, number of eosinophile cells ; this eosinophile infiltration extends quite deeply down into the subcutaneous tissue. They not only occur in, and around the vessels, but form chain-like rows between the connective tissue elements. In the papillary part of the corium there is a moderate infiltration by lymphocytes. At this stage the vessels exhibit nothing abnormal.

1 *day*. *Macroscopically*. Appearance normal.

Microscopically. The epidermis very closely resembles that of the one-hour specimen, there are, however, fewer lymphocytes and no eosinophiles. In some places the parallel arrangement of the palisade layer is lost, but in general the cells are normal in arrangement and appearance. The corium shows an increase in the number of lymphocytes ; sometimes these are grouped into clumps, at others discretely scattered. The eosinophiles are less numerous than in the preceding specimen (1 hour), in the subcutaneous tissue only occasional examples are to be seen, and the lymphocyte infiltration is small ; fibroblasts occur occasionally, as do also polymorphonuclears in the papillæ. The capillaries in general are well filled with blood, but here and there branches are noted which contain only closely packed leucocytes.

2 *days*. *Macroscopically*. A slight yellowish pigmentation about .5 sq. cm. in area.

Microscopically. The epithelium is raised in places, but generally is kept in place by the hair sheaths. The deeper layers near the corium exhibit definite inflammatory changes, with, in places, cleft-like spaces which are filled with polymorphonuclears. These cells also occur in the corium, though in less numbers. The thickness of the epidermis is diminished in the irradiated

areas, but individual cells occasionally appear swollen, while the deepest layers of the epidermis show such a degree of leucocyte infiltration that the structure of individual cells is obscured. In the hair sheaths are groups of polymorphonuclears. The corium shows infiltration which is most marked in the layers immediately subjacent to the epithelium. The subcutaneous tissue shows a marked degree of perivascular infiltration, mostly of lymphocytes, but eosinophiles are also present. The capillaries and small vessels show endothelial changes, with consequent narrowing of their lumen, and their walls are infiltrated with leucocytes. Deeper, in the muscles and in the neighbourhood of nerves and vessels, are numerous eosinophiles, sometimes occurring singly, and sometimes in groups. In the corium, on the other hand, this type of cell is less numerous than in the preceding specimen (1 day).

3 *days*. *Macroscopically*. A pale yellow area, identical in size with the preceding specimen (2 days); the surface is somewhat raised, the hairs are well fixed and not easily pulled out.

Microscopically. The epithelium is distinctly raised by exudate, but still anchored by the hair sheaths. In the centre of the irradiated area the nuclei of the epithelial cells are unstained; they are also shrunken and seem to lie in brightly stained spaces. In the deeper layers of the epithelium, in the neighbourhood of the numerous infiltrating leucocytes, are chromatin fragments, sometimes they occur free, at other times in the leucocytes themselves.

The corium, in its papillary part, shows an extreme degree of leucocyte infiltration, and forms a sort of leucocyte-filled edge which is marked off into tolerably regular sections by the hair sheaths. The small "erectores pilorum" muscles ascend from the deeper layers, and disappear in this leucocyte-crowded border. The vessels of the corium are congested and show endothelial changes.

5 *days*. *Macroscopically*. There is now a raised dry brown scab, with an area of about .5 sq. cm.; this fixes the hairs in its own area, but in the surrounding zone of about 2 mm. in width the hairs have partly fallen out.

Microscopically. The cell-nuclei of the raised epithelium do not stain, but lumps of chromatin occur extra-cellularly. Since the hair sheaths ascend obliquely, one side of them has been more

exposed to the rays than the other; the effects of this are now seen, since the epithelial cells of the sheath only persist in the less irradiated side of the sheath. In the corium the vessels of the papillæ are engorged and local hæmorrhages can be noted. The hairs are broken away by a broad band of infiltrating leucocytes (mostly multinucleated) mixed with red-blood corpuscles and fibrin, by means of which a layer of the corium itself is raised and separated from subjacent parts. In this separated layer the connective tissue nuclei do not stain, and the only indication of connective tissue which remains is a number of bundles of fibres, which stain well with eosin, and which are mixed with leucocytes and chromatin débris. The vessels in the deeper parts of the corium and subcutaneous tissue show engorgement and degenerative changes. The muscular tissue is well preserved, but the bundles of muscle fibres are frequently separated by the leucocyte infiltration in the neighbourhood of the engorged vessels. The large number of eosinophile cells in this situation forms a striking feature of the picture.

7 *days. Macroscopically.* As before.

Microscopically. The epithelium has disappeared in the irradiated area, the remains of hairs can be detected, and even in the deep parts of the corium the cells of the hair sheaths have completely disappeared. The denuded upper part of the corium shows infiltration by leucocytes and a large amount of fibrin, the nuclei of the original connective tissue cells do not, however, stain. At the periphery of the ulcer a small ingrowing layer of squamous epithelium can be seen growing in under the necrotic mass. The peripheral non-irradiated epithelium is definitely thickened, the cells increased in number and staining clearly. The remaining features are much like those of the preceding specimen, except that the large infiltration of eosinophile cells in the muscular tissue has now disappeared.

9 *days. Macroscopically.* Depilation is more marked, the other appearances as before.

Microscopically. Much the same as before, the thickening of the epithelium at the periphery is, however, more marked.

11 *days. Macroscopically.* The scab is a little larger.

Microscopically. The young ingrowing epithelium has still further intruded itself under the raised scab. The papillary part of the corium shows lamination, owing to infiltration by round-

cells, fibrin and exudate. In the subcutaneous tissue there is a marked increase of connective tissue nuclei.

The vessels exhibit the same changes as in previous specimens, but are not so engorged. In the arteries which show a marked degree of endothelial disintegration, the number of red-blood corpuscles is diminished while that of the leucocytes is distinctly increased. In the subcutaneous tissue the arteries show a marked change; the endothelial cells are so swollen and irregularly

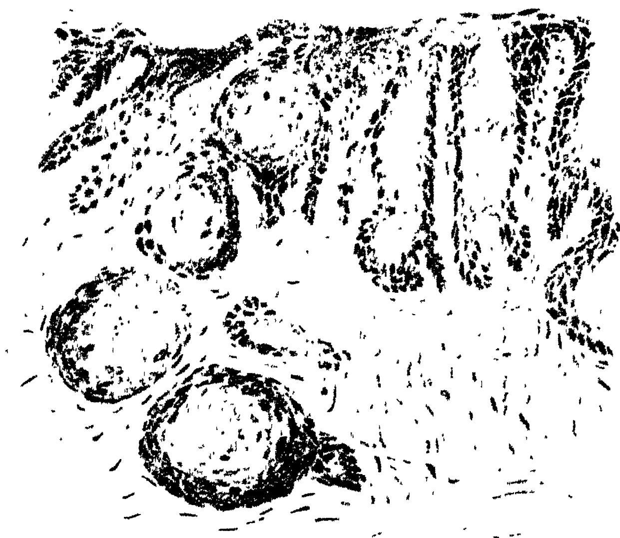


Fig. 22.—Hypertrophic changes and cell-nest formation in skin of guinea-pig resulting from exposure to radium (*vide* p. 177).

arranged that the lumen of the vessel is constricted to a degree which almost completely arrests the circulation, and as a consequence may be practically empty of blood. At the periphery of the irradiated area, the epithelial hypertrophy is well marked. Large downgrowths invade the subjacent tissue, and frequently enclose round or oval bodies which contain many nuclei. The protoplasm stains with eosin, but the structure is obscure, so it is difficult to say if they are giant cells, or cell nests as seen in carcinoma. The marked invasion of the tissues by irregular processes of cells would seem to favour the latter hypothesis.

14 *days. Macroscopically.* The scab has disappeared, and the irradiated portion is dry and devoid of any secretion.

Microscopically. There is a general disappearance, centrally, of connective tissue elements. The part of the corium that remains is full of leucocytes and nuclear débris. The changes in the vascular endothelium are still well defined. The thickening of the peripheral epithelium has still further progressed ; the processes have increased in size, isolated islands or cell groups can be seen and there are definite cell nests.

A good instance of the hypertrophic changes arising as a consequence of exposure to radium is that illustrated in Fig. 22, which shows a marked hypertrophy of the epidermis with the formation of cell nests in the skin of a guinea-pig, after an exposure of 6 hours to the gamma rays from 20 mgs. radium bromide.

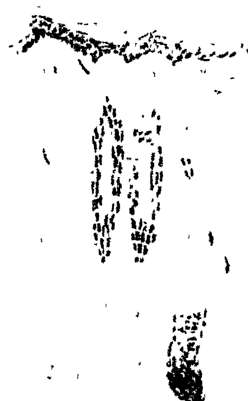


Fig. 23
Control to Fig. 22.

Dominici, working in conjunction with Barcat, made a series of experiments with the object of demonstrating the different effects produced when a radium preparation is screened and when it is applied directly to the surface of the skin. In the case of the unscreened apparatus they used a varnish applicator of 2 cms. diameter, and containing a little more than 6 mgs. of radium sulphate. Guinea-pigs were the animals employed in these experiments, and daily exposures of 5 minutes were given for ten consecutive days. In this series of observations there was, of course, neither mica nor aluminium covering to the radium salt, which was simply covered with a thin layer of varnish.

Ten days after the commencement of the exposures the skin showed distinct redness ; towards the third week an ulcer was formed which was covered with a scab, which fell off between the fifth and sixth weeks, leaving a scar, white, devoid of hair and of supple consistency.

Histological examination of exposed area eight or ten days after the commencement of exposure. The epidermis showed changes of an inflammatory character, characterised by modifica-

tions in the epidermal cells themselves and by the presence of intercellular œdema. The cells showed signs of hypertrophy, both as regards the nucleus and the cytoplasm. The nucleus, in addition to enlargement, also manifested irregularity of outline, together with thickening of the chromatin fibrils and of the nucleolus.

From the fifteenth to the twentieth day there was epidermal desquamation, together with marked degenerative changes in the hair follicles and in the sudoriferous and sebaceous glands.

Changes in the dermis. The dermis in the irradiated area was found to be the seat of well-marked and characteristic changes. Dominici calls attention to two phases in these alterations and terms them :

(*a*) The phase of embryonic regression.
(*b*) The phase of fibrosis.

The phase of embryonic regression. The dermis is the site of an intense congestion and of the early stages of "embryonic transformation." An examination made thirty to forty days after the commencement of the experiment, reveals the renewal of the epidermis, though the hair follicles and glandular structures are completely destroyed. The dermis, on the other hand, has undergone such changes that its normal structure is practically entirely lost. The connective tissue bundles and the elastic fibres have nearly disappeared, and have given place to very numerous fusiform, branching, connective tissue cells. The cellular processes anastomose, so that a plexus is produced, of which the meshes are long, fusiform and narrow. Dominici regards these cells as the fixed connective tissue cells, which have not only undergone proliferation, but have also reverted to the embryonic type. The characteristic features of these modified cells are the marked increase in their cytoplasm, and a hypertrophy of the nucleus, which is even more marked than that of the cytoplasm. The result of this hypertrophy, taken in conjunction with a large development of processes and their anastomoses, is that the tissue shows a marked preponderance of the cellular over the fibrous constituents. So marked is this that the fibrous bundles and elastic fibres seem to have been almost completely replaced by these enlarged branching cells.

The non-striated muscular fibres undergo such a metamorphosis that they are indistinguishable from the changed fixed

connective tissue cells. The small blood-vessels also show changes, in the direction of a reversion to embryonic forms. Their coats are reduced to a collection of fusiform and stellate cells continuous, on the one hand, with the proliferative connective tissue cells, and on the other, with the endothelial cells of the vessels themselves. These endothelial cells, in their turn, acquire the plasmodial characters of the embryonic type, and form a continuous hollowed protoplasmic cylinder, dotted with large nuclei. In many places these modified vessels give off branches, which



FIG. 24.

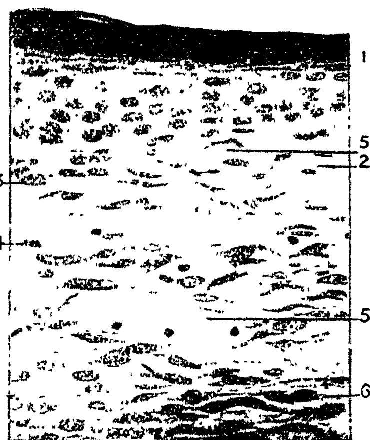


FIG. 25.

FIG 24—Section of normal skin of guinea-pig. Control to Fig. 25. E, epidermis. D, dermis. 1, cells of the epidermis. 2, connective tissue cells. 3, muscular fibre bundles 4, hair-bulbs 5, blood-vessel.

FIG 25.—Section of skin of guinea-pig showing embryonic transformation of cells subsequent to exposure to radium. 1, epidermis. 2, 5, dilated blood-vessels with embryonic characters 3, 4, 6, matrix consisting of cells which have taken on embryonic characters.

(Dominici, *Arch. Générales de Médecine*, pp. 404-502. 1909.)

again in turn branch and anastomose freely. The result of these modifications of the connective tissue and vascular system of the dermis is their conversion into tissue of an embryonic and angeiomatous type. This state of affairs is however transitory, and is succeeded by the re-development of fibrous connective tissue.

The phase of fibrosis. In this stage the calibre of the blood channels undergoes diminution, while the connective tissue cells gradually lose their embryonic character and form connective tissue fibres, the general trend of the whole phase being towards

the formation of a fibrous scar. This scar, however, differs from the scar tissue formed as the sequel to ordinary inflammatory processes, and also from the normal non-irradiated dermis. It is distinguished from ordinary post-inflammatory fibrosis by the extraordinary regularity of its structure ; the bundles of fibrous elements are separated from one another by the elongated fibroblasts, so as to form a series of layers, parallel to one another and to the surface. The whole picture is forcibly reminiscent of the appearances of a young and actively growing fibroma. The fibroblasts are numerous, and in places may preponderate over the fibrous elements themselves. The scar-tissue differs from a fibroma in that it does not exceed, or tend to exceed in volume, the normal tissue which it replaces. As development proceeds, it is converted into fibrous tissue, characterised however, by the presence of an unusually large number of elastic fibres.

Six or seven months from the commencement of the exposures, the cellular elements have very largely given place to connective tissue fibres, although the remarkably regular arrangement of the remaining fibroblasts and the bundles of fibres affords a difference from the structure of normal corium, and resembles a fibroma in the parallel arrangement of connective tissue cells and fibres.

To sum up : after 50 minutes' exposure to the unfiltered rays, as described on p. 165 the final results are :

(1) Permanent destruction of the hair follicles and sebaceous and sudoriferous glands.
(2) Temporary destruction of the epidermis.
(3) A temporary reversion on the part of the corium to an embryonic type. This, though of considerable duration, is followed by a definite fibrosis, characterised by a remarkably parallel and regular arrangement of the fibrous and cellular elements.

The effects of filtered rays upon the skin. If the radium applicator is screened by the interposition of .5 mm. of lead, covered by a layer of paper and a thin layer of rubber protective, the results are different.

After 50 minutes' exposure no changes whatever can be observed.

After 14 hours the only results are an enlargement of the nuclei of the epidermal cells, temporary loss of hair, and some congestion in the dermis, accompanied by a slight increase in

size of both nucleus and cytoplasm of the fixed connective tissue cells.

After an exposure of from 2 to 3 days there is superficial and transient destruction of the epidermis; while in the corium the typical bi-phasic change occurs, similar to that obtaining from exposure to the unscreened preparation for 50 minutes.

In 1909 Guyot published an account of an exhaustive series of researches upon the action of radium on the skin. The animals employed in these experiments were white mice from four to six months old; they were enclosed in a small lead covered box, and subjected to irradiation by means of an aperture in the lead. The skin of the animal was distant 1.5–2 cms. from the mica face of the radium capsule, which contained .1 gram of radium bromide.

The exposures were in all cases made for 48 hours, and a series of specimens was obtained showing the histological appearances at different periods after the irradiation.

General remarks and macroscopic appearances. The general condition of the animals was good, and they maintained a normal weight. For the first few days after exposure no changes were visible, but towards the end of the first week some demarcation of the irradiated area occurred. At this period the surface appeared paler than normally, owing to the presence of scales, consisting mostly of sebaceous material; these gradually increased in number. In the second week active desquamation of the epidermis occurred; many of the hairs fell out spontaneously, while others came away, together with the desquamated epidermal flakes, at the slightest pull. The depilation increased and was quite definite, between the fifteenth and twentieth days. At the same time a definite inflammatory reaction was plainly visible on the surface, which was now denuded of seborrhœic scales and hairs; the skin was reddened, and exuded drops of serum which subsequently dried and formed yellowish crusts. The exudate soon contained blood, and extensive scabs were thus formed. Between the thirtieth and fortieth days this scab fell off, leaving a raw ulcerated surface; the exudate soon produced a new scab, and at this period (thirtieth to fortieth day) the alopecia was at its maximum, as subsequently new hairs began to make their appearance. Towards the end of the second month this second scab came away, and a small quantity of blood-stained foetid pus

exuded. New scabs were formed, and towards the end of the third month the further changes became definitely reparative in character. Healing occurred with the formation of a dense thick scar, reddish at first, but subsequently becoming whiter. Towards the end of the fourth month a few tufts of sparse fine hairs appeared; the hairs gradually increased in number until the area was fairly covered; but even in an animal in which complete healing had existed for a period of seven months, the site of the irradiation was clearly distinct from the surrounding skin.

Microscopic. For purposes of description the different cutaneous structures will be considered seriatim.

I. The Epidermis. (1) *Normal epidermis of the mouse.* The normal epidermis of the mouse consists usually of a single layer of more or less cubical cells, and over this a thin stratum lucidum and stratum corneum. Sometimes there are two layers of the deepest or cubical cells, instead of as is more frequent, the single layer mentioned above.

(2) 3 *days after irradiation.* The epidermis generally presents a perfectly normal appearance. Here and there, however, the deepest or cubical layer of cells has undergone proliferation and formed a double layer. In this case the deeper cells are larger than normal, have an oval nucleus and clear homogeneous cytoplasm. This thickening is not uniform all over the section, but forms little plaques or epithelial nodules, where occasionally the single layer of cubical cells has increased to four or five layers. The stratum corneum is also somewhat thickened, and shows an increase in the number of lamellæ which compose it.

5 *days.* In the centre of the irradiated area there is a marked thickening of the epidermis, where it is four or five times as thick as normal. On passing peripherally from the centre this thickening is seen to diminish, and at the edges of the section the epidermis is barely twice its normal thickness. There is, however, no graduation in this change, but thick zones alternate with those of less thickness. The fact, however, remains, that the epithelial thickening is most marked in the centre of the irradiated area, and that it diminishes, though irregularly, towards the periphery. The increase of thickness is due to increased cell proliferation in the deeper layers, and also to an increase in the number of layers composing the stratum corneum.

In these islands of thickening the cells have lost their normal

appearance. The cells of the deepest layers, instead of being cubical, have become cylindrical, and are arranged in a palisade-like manner; their protoplasm has become granular, and the nucleus is clear and bright, with distinct nucleoli.

The superficial cells are flattened, their nuclei stain darkly, and are elongated or oval. Between these two cell types various intermediate stages can be observed. At the points where the hair sheaths join the epidermis, it can be seen that they also have undergone thickening (see p. 183).

10 *days*. This specimen closely resembles the preceding, but the epithelium is more generally thickened over the whole area, as a rule to about twice its normal thickness. Indications of the changes which will be seen in subsequent specimens have, however, begun to show themselves; for in addition to the thickening just mentioned, and the presence in places of islets of more pronounced thickening, the epithelium is very definitely thinned over certain areas.

14 *days*. In these specimens the loss of epithelium is very marked. In places no trace of epithelial cells is to be seen, and the surface is covered with nodules consisting of leucocytes, fibrin and blood, together with a large number of bacteria. In other places where the epithelium has not completely disappeared, it is only represented by a few thin elongated cells, irregularly disposed and not forming any definite layer. These cells show marked keratohyaline degeneration, and also marked variations in size; so that among cells which are much smaller than normal there also occur larger forms, and indeed true mononucleated giant cells. In situations such as these it is plain that the epidermal changes are of an atrophic variety. At the periphery of the irradiated area the epidermis will, on the contrary, be found to have undergone definite hypertrophy. Here the stratum lucidum is well developed, as are also the corneum and granulosum. The deepest layers have the palisade-like arrangement, and here again there is evidence of hyperkeratosis.

19 *and* 20 *days*. The specimens obtained at this period closely resemble the preceding. The horny layer is reduced to a few flattened cells with pycnotic nuclei; their protoplasm has a vitreous appearance and contains eleiden granules. In places the epithelium has totally disappeared, and only the superficial horny laminæ cover the cutis. At the periphery of the irradiated area

the epithelium is markedly thickened, and shows evidences of abnormal proliferation.

25 *days.* In the central parts are traces of the scabby crust; in places the cutis is completely exposed, or practically covered with a layer of keratohyaline material, which is all that remains of the keratinised and exfoliated epidermis.

At the margins, on the other hand, the epithelium is seen to have undergone luxuriant growth. This growth especially affects the stratum lucidum and the stratum corneum; in the superficial layers marked keratohyaline involution is conspicuous.

At this stage the first signs of regeneration of the hairs are noticed, together with a cystic dilatation of the sebaceous glands. The whole epithelium has the appearance of a metaplasia, and presents appearances similar to those observed in certain cutaneous new growths.

37 *days.* This specimen, obtained from an animal which died spontaneously from marasmus and pneumonia, shows a complete disappearance of epidermis in the situation of the scab. Some thickening of the epidermis is noticeable in the more peripheral zone, but the changes as a whole are less marked than are those in the preceding specimen.

45 *days.* The scab which formed after the irradiation has now fallen off and been replaced by a second one a trifle smaller than the original. The general changes observed are of a definitely reparative character. Centrally there is an absence of epithelium beneath the scab, but at the periphery it is thickened and projections extend downwards into the cutis. Still more eccentrically it merges by a series of graduations into the normal epidermis.

70 *and* 71 *days.* The second of these specimens was obtained from an animal which died from marasmus. The seventy-day specimen still shows epidermal thickening, but it is less marked than in the forty-five day specimen. The seventy-one day specimen shows less reaction than would be expected (cf. the thirty-seven-day specimen).

95 *days.* Complete healing has occurred. The section shows a scar area, and a surrounding zone where the original alopecia has begun to be repaired by the development of new hairs. The epidermis still shows definite hypertrophy and projects in places down into the cutis.

4 *to* 5 *months.* There is still a moderate degree of epidermal thickening, but it is less marked. The region surrounding the scar shows a gradual return to the normal condition.

Summary of the preceding changes in the epidermis. *In the central zone.* Already, on the third day, epidermal proliferation occurs, and is due to the formation of plaques and nodules. This process rapidly increases up to the tenth day, so that the epidermis is several times thicker than normal. After the tenth day this hypertrophy is slower, and is characterised by a process of cellular involution associated with hyperkeratosis.

In the peripheral zone. Epidermal proliferation also occurs, but is slower in making its appearance, commencing about the tenth to the fourteenth day. It lasts from sixty to seventy days, and is associated with changes producing the characters of a definite metaplasia. The epidermis in this situation is not lost, and regains its normal features without denuding the corneum.

II. The cutis. The cutis normally consists of fibrous tissue with relatively few cells, and among these are some elastic fibres, especially in the neighbourhood of the follicles. The whole cutis is well supplied with blood- and lymph-vessels.

Two or three days after irradiation there is a marked increase in the number of nuclei, and the fibrous elements appear swollen. About the fifth day the cellular infiltration is more definite. This consists mainly of proliferating connective tissue cells, but in addition wandering cells are present, having escaped from the dilated vessels. Simultaneously with these changes a serous exudation occurs, so that considerable thickening of the whole cutis is apparent. Concomitantly with these exudative and infiltrative changes occurs a destruction of the epidermis, which subsequently separates, leaving an ulcerated surface. After the ulcer has formed, the section shows the presence of cellular débris, extravasated blood, fibrin and various forms of bacteria. With repair the exudative elements diminish, and young granulation tissue predominates. The "erectores pilorum" muscles which traverse the cutis obliquely offer considerable resistance to the destructive effects of radium, since they can be demonstrated in the midst of the inflammatory changes, provided, of course, that the ulceration has not extended to such an extent as to cause complete local destruction. When complete healing has occurred the repaired cutis is more compact than normal, and contains more

fibrous elements. The elastic fibres are highly resistant, and the blood-vessels show the typical changes.



Fig. 26.



Fig 27

Fig. 26.—Metaplastic hypertrophy of irradiated skin of mouse, para-central zone, 26 days after exposure.

Fig. 27.—Hypertrophy of epidermis and sebaceous glands, with cystic formation of latter.

III. The sebaceous glands. On the fifth day a definite enlargement of the sebaceous glands is evident. In the more advanced

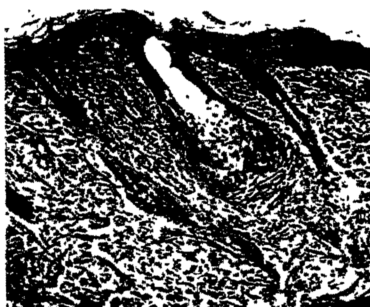


Fig. 28.



Fig. 28a.

Figs. 28 and 28a.—Hypertrophy and hyperkeratosis of epidermis of mouse 14 days after irradiation. (*Archiv f. Dermatologie u. Syphilis.* 1909.)

stages where the cutis is eroded they will be found to have disappeared, but they occur plentifully around the ulcerated surface. On the twenty-sixth day, in the region surrounding the ulcerated area, numerous enlarged sebaceous glands are to be seen, some of

which have become cystic. In some cases these cystic cavities still maintain their connection with the surface, while others form true closed cysts. The cells of the dilated gland cavity show degenerative changes, partly, no doubt, due to the direct action of the radium, but also as a result of the pressure to which they are subjected by retained secretion.

When total disintegration of gland tissue has taken place, regeneration occurs from the columns of epithelial cells from which the hairs originate. From forty-five to seventy days after irradiation reparative changes are seen side by side with degenerative phases, and the two conditions are often difficult to differentiate. The newly-formed glands rapidly increase in size, and acquire in many cases the character of the hypertrophied glands of the peripheral zone.

IV. The hair. The first definite changes in the hair appear about the fifth day. The cells of the outer root-sheath are then seen to be swollen and somewhat rounded, and show proliferation continuous with the general proliferation of the epidermis. Some thickening of the lower part of the hair follicle occurs as the result of leucocyte invasion. About the fourteenth day the initial hyperplasia of the outer root-sheath is accentuated, but from this time to the twentieth day the cells composing it undergo keratinisation and involution. Keratinisation and atrophy of the bulb are also noticeable. As the process of degeneration progresses, the follicle becomes converted into a fibro-cellular strand, occupying the position of the hair which has disappeared, while the papilla is represented by a mass of round cells.

Formation of new hair may occur in one of two ways, regeneration or complete new formation. Regeneration from vestiges of the original structures only occurs in the less strongly irradiated peripheral parts. It takes place from the remains of the hair bulb or of the root-sheath. New formation of hair is characteristic of the centre of the irradiated part, and is caused by downgrowths of the epidermis covering the scar area.

Histological appearances of irradiated normal human skin. Specimens of irradiated normal human skin are, of course, difficult to obtain for histological examination. Thies, however, irradiated an area on the back of his own forearm for 1 hour, and extirpated it after ten days, using the same 20 mgs. capsule as in his other experiments. Reddening was noticed on the third day and had

become darker on the tenth. The microscopic appearances were similar to those seen in the guinea-pig on the second or third days after a 6 hours' irradiation (see p. 169). There is some thickening of the epidermis, but the cells of the deepest layer have lost their normal palisade arrangement, some even lying at right angles to their normal position, and the nuclei are irregular in size. Between the individual cells of the epidermis is an invasion of lymphocytes, which is especially marked in the deepest layers. The nuclei of the cells in the centre of the irradiated area stain badly, but the cell outlines are well preserved; in some places the stratum corneum has undergone thickening.

Latent period. It was early noticed that a period of time elapses between irradiation of the skin by radium and the production of any visible effect. Halkin (1903) in his observations upon the irradiation of the skin of young pigs, found that with a 2 hours' exposure to a 130 mgs. capsule, this period was eight days; while, with an exposure of 1 hour only it was fifteen days. He further noted that with the shorter period of exposure, the resulting lesions were less severe and passed off sooner.

Goldberg (1903) also irradiated young pigs (two weeks' old) and found that the latent period was shorter, with larger amounts of radium and longer exposures. His results may be tabulated thus:

TABLE 45.

Quantity of Radium.	Time of exposure.	Latent period.	Time of exposure	Latent period.
75 mgs. -	1 hour	5 days	2 hours	2 days
30 ,, -	,,	5 ,,	,,	3 ,,
25 ,, -	,,	6 ,,	,,	—
7·5 ,, -	,,	15 ,,	,,	—
5·0 ,, -	,,	—	,,	15 ,,

In addition to these animal experiments, Goldberg also irradiated the skin of the front of his forearm. The exposure was given for 3 hours, the amount of radium bromide being 75 mgs. On the third day there was redness at the irradiated spot, and a blister soon appeared. On the fifth day the surface became ulcerated. For some months the ulcer showed no tendency to

heal, but eventually slow healing occurred, and there was marked increase in the amount of hair surrounding the scar. In this connection reference may be made to the clinical data of Werner and Hirschel (1904), who published the results of their treatment of twenty-two patients by radium. Various superficial lesions were treated, such as malignant cutaneous growths, lupus and nævi and in their report on the results obtained, they give the amount of radium used (10 mgs.), the duration of exposure and the length of the latent period.

The Report of the Radium Institute, London, which appeared in 1913, contains some information concerning the effects of the rays from radium upon human skin, and the data have especial value as having been derived from observations upon a large number of cases. The following passage is taken directly from this Report.

"The reaction usually appears between the 7th and 15th days, and may vary in character from a slight erythema to a destructive ulceration. Four degrees may be clearly distinguished:

(1) Simple erythema.
(2) Erythema followed by desquamation.
(3) Vesication with superficial ulceration.
(4) Deep ulceration; sometimes accompanied by the production of an eschar.

"With some patients the time of reaction is much delayed, with others the response is exceedingly prompt, and it is difficult, if not impossible, to say why this difference should be. It is particularly noticeable in the treatment of capillary nævi, and cases have been seen in which, instead of the reaction appearing on or about the 7th or 8th day, it has been evident 3 days after exposure. In others a period of four weeks has elapsed before any effect has been perceptible, though in all of these cases the applicators employed, the screening and the times of exposure have been identical."

This question of personal idiosyncrasy we shall return to in Chapter XVIII.

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GAMMA RAYS UPON NORMAL TISSUES

A detailed Report has recently been issued by the Medical Research Council Radium Report No. 1 (1922), upon the effects of the gamma rays from about 5 grams of radium bromide upon the normal tissues of frogs, rats, rabbits and cats.

The subject is much too extensive for detailed consideration here, and readers are referred to Article No. 3 in this Report, entitled " On the Histological and some other Changes produced in Animals by exposure to the gamma rays of radium," by W. S. Lazarus-Barlow.

X RAYS

That the X rays are capable of producing very marked effects upon the skin was unfortunately soon made manifest to the pioneer workers in radio-therapy. Painful forms of dermatitis, with loss of hair and nails, were not the worst of the troubles to be apprehended, since these in many cases were followed by deep and slowly-healing ulcers. Rodet and Bertin-Paris in 1898 drew attention to the very extensive skin lesions, such as dermatitis, loss of hair, and the extensive wounds which may result from excessive exposure to the rays. Experimental work upon animals had already been undertaken by Oudin, Barthélemy and Darier, who in 1897 recorded the results obtained by exposing guinea-pigs to the rays. In these animals a marked hyperplastic dermatitis was produced ; the epidermis underwent great thickening in all its layers, and a special feature of the changes was the very marked increase in the eleidin content of the cells and the disappearance of hair and of sebaceous and sweat-glands.

Unna in the same year described certain changes in the histological appearances of irradiated human skin when sections were treated with his orcein, acid-fuchsin and picric acid stain. Normally the collagen-containing elements—white fibrous tissue —when stained by this reagent are red, but in the irradiated samples they took the orcein stain strongly. As Unna expressed it, the collagen had become " basophile."

Gassmann, in investigating the histology of an X-ray ulcer, found in addition to various inflammatory changes, that the endothelial cells lining the larger blood-vessels of the cutis and subcutaneous tissue had undergone degenerative changes in the shape of swelling and vacuolation.

Lion in 1901 examined sections of healthy skin, which had been subjected to only a slight degree of irradiation and presented no macroscopic changes; the only histological deviation from the normal type was some " loosening " of the compact palisade-like layer of the epidermis. An X-ray burn was described by the same observer as having the epidermal cells swollen, vacuolated and separated from one another by irregular spaces, while the endothelium of the blood-vessels showed proliferation and vacuolation.

In 1902 Scholtz published the results of his investigations: the experiments were mostly carried out on young pigs, though in some cases rabbits were used. The earlier series of observations were directed to the question of the relative value of " hard " and " soft " tubes; and it was found that the most marked effects upon the skin were obtained with the softer types of rays.

It had been shown by Revillet, Kummel and other clinical observers that the influence of the rays is not confined to that area of skin upon which they impinge from the bulb, but in passing through the body produce definite changes upon the skin of the opposite surface. These results were confirmed by Scholtz in his experiments upon the ears of rabbits and pigs; he further concluded that the skin suffered in far greater degree than other tissues, such as muscle, cartilage and bone. The following data in connection with his experiments are of interest.

(1) *Skin of Back.* Irradiation for 1 hour, bulb 20 cm. distant from skin. Skin examined 24 hours later. Macroscopically no alteration, microscopic appearances normal, except that the

prickle cells stain somewhat more darkly and diffusely than normal, and their contour is not so well defined.

(2) *Skin of Back.* Irradiated as before. Skin examined 7 days later. Macroscopically there was some loosening of the hair, but no other abnormality. Microscopically the stratum corneum is less compact than normal; the prickle cells show marked changes, being swollen and of indefinite contour; the cytoplasm is vacuolated, and the nucleus shows disintegration of its chromatin; similar changes are found in the cells of the palisade layer, but, as the surface is approached, the changes in individual cells become more and more difficult to determine as their contour becomes indistinct and their protoplasm seems fused into a more or less homogeneous mass. In the cutis marked œdema and general appearances of inflammation are present, and the connective tissue cells show slight degrees of change. The cells of the sweat glands are degenerated, and in some cases have undergone proliferation into the lumen of the gland. The endothelium of the blood-vessels is vacuolated and degenerated.

(3) *Ear.* Irradiation 11 times for 15 minutes, bulb 15 cm. distant. Skin examined 6 days after the last exposure. Macroscopically there is depilation on both surfaces, and the skin looks reddened and atrophic. The microscopic findings are much the same as in the previous specimen, but the fused and homogeneous appearance of the cells of the upper layer of the epidermis is still more marked. There is a marked invasion of leucocytes, and the signs of inflammation are very pronounced. The cells of the hair bulbs and sheaths are degenerated and separated from one another by invading leucocytes.

(4) *Skin of Back.* Irradiation 9 times for 15 minutes, bulb 15 cm. distant. Examined 8 days after the last exposure. Macroscopically there is a well-marked "burn" covered with a thin layer of purulent and fibrinous material. Microscopically there is complete destruction of the epidermis down to the rete Malpighii, their place being occupied by masses of polynuclear leucocytes with pus cells and fibrin mixed with masses of bacteria and cocci. The vessels show profound degenerative changes in their endothelial cells, but elastic fibres, wherever present, are apparently unaffected.

Gaucher and Lacapère drew attention in 1904 to the fact that if X rays be applied to the human skin in too large quantity,

they produce a burn varying in intensity from a reddening of the skin to an ulceration appearing a few days (6–10–14) after the exposure; such they consider to be the true examples of acute radio-dermatitis.

If, however, very small doses are given extending over a long period, quite a different result is produced, namely, chronic radio-dermatitis. These authors submit that the condition would be more appropriately called neuritis, as the lesions are really due to the action of X rays upon the nerves. The symptoms of two human cases which they were able to study pointed to the existence of severe nervous lesions. They point out that these chronic conditions are associated with a hypertrophy of the different layers of the skin, leading to the formation of papillomata, which in turn may become malignant. Subsequent observations have shown that this distinction is a real one, and the fact illustrates in a striking manner the different effects associated with a large quantity of radiation acting for a short time, and a small quantity acting over a prolonged period; this is a consideration to which we shall return.

Rowntree in 1909 brought evidence to show the effects of prolonged exposure of the tail of the rat to X rays. A transverse section of a rat's tail, after being irradiated, may be considered as made up of three zones: (*a*) the dorsal surface, presenting advanced dermatitis; (*b*) the ventral surface exhibiting no departure from the normal; (*c*) the side portions of the tail, showing at some places a hypertrophied condition, suggesting a stimulating action of the rays locally.

Rowntree extended his observations to rabbits; after irradiating their ears for periods corresponding to 1 or 1½ pastille doses, he studied the subsequent changes which occurred. These included the gradual falling out of the hair, followed by desquamation, which ended in ulceration of the irradiated surface. Similar indications of hypertrophy in the less irradiated regions were obtained as in the case of the rat already referred to.

Menetrier and Mallet, by irradiating the ears of white rats, obtained not only epidermal proliferation, but also definite evidence of a condition of metaplasia, such as abnormal keratosis and the formation of epithelial cell nests.

Clunet illustrates a metaplastic hypertrophy of the skin in the human subject, produced by repeated irradiations during

the treatment of a tumour in the thyroid gland, the skin prior to the treatment being apparently perfectly healthy. After exposure to X rays had been continued for several months, a chronic hypertrophic radio-dermatitis was set up; the hypertrophy extended to as much as 40 layers of living cells in the epidermis, with a papillomatous down-growth (*vide* Plate III.).

In concluding this section, attention may be called to a salient fact gleaned through years of the clinical application of X rays to the human skin; the reaction of the skin to soft X rays is of an entirely different character to that provoked by hard X rays. The application of more than a Sabouraud pastille dose (1B) of soft X rays to the human skin is dangerous; (2B) is almost certain to produce a disturbance amounting perhaps to a radio-dermatitis. If, however, the rays are filtered through about 4 mm. of aluminium, the skin may receive a much larger dose without any attendant danger. In attempting to find some rational explanation of this remarkable fact, we shall do well to enquire somewhat more closely into the terms "soft" and "hard"; when measurements are made upon the penetrating power of a typically soft and hard radiation from an X-ray bulb, it is found that the "hard" rays have easily 7 or 8 times the penetrating power through aluminium that the "soft" rays have. By means of the simple relation found by Owen and by Moseley and C. G. Darwin, connecting the wave-lengths of X rays with their penetrating power, we may say that the wave-length of the "soft" rays is more than twice that of the "hard" rays (*vide* Table 4, p. 27). The scale of these wave-lengths is about 10,000 times smaller than that of the visible spectrum, and it seems that, as in the one case so in the other, a change in wave-length may give rise to an entirely different response on the part of the living cell.

The difference in reaction of the human skin when made to absorb equal amounts of "soft" and of "hard" X rays was the first instance recorded of the biological effects of the rays being dependent upon the wave-length of the X rays used. This is referred to in Chapter XX. as the "differential" effect of the rays.

It must not, however, be inferred that the more penetrating X rays are without effect upon the skin; if the dose administered be large enough harmful action will result. It is a remarkable thing that some of the effects upon the skin after highly filtered

X rays have been used only appear a long time, in some cases years, after the exposure to the rays. Spéder has called attention to this matter, and remarks upon its comparative rarity; it does not appear possible to predict in any way the type of case which is likely to give this late reaction. Spéder considers that these delayed reactions are due to a destructive action of the rays upon the walls of the arteries. Finzi, who records several cases of these "late X-ray burns," as they are sometimes called, inclines to the view that they are really due to different types of infection in tissues, which have initially been damaged by exposure to the rays.

Such facts suggest that ' selective absorption " plays some part in conditioning the response of the cell to irradiation. When the attempt is made to find whether the various types of cells forming the skin do actually exert a selective absorption upon soft X rays, experimental difficulties make their appearance. If such "selective absorption" occurred only in certain parts of the cells, the ordinary absorption measurements would give little or no indication of the action which locally might exist. Barklas' investigations on characteristic X Rays (p. 18) would lead us to attribute any such effect, if it existed, to the chemical constituents other than the light elements, hydrogen, carbon, nitrogen and oxygen. Tissues of the same histological structure may vary in their mineral content to a sufficient extent to give the different reactions observed. Although one may doubt the complete validity of the law formulated by Bergonié (p. 280), it is nevertheless a cogent fact that rapidly-growing tissues are often very sensitive to irradiation; if it could be shown that in the metabolism of such tissues an enhanced mineral content played a part, a step towards explaining this particular sensitiveness might be attained.

The skin reactions which follow the external application of radium or X rays frequently set a limit to the amount of radiation which can be so applied. Seeking to get an intense dose of radiation to a tumour-mass at a depth below the skin, the radiologist has this consideration frequently before him; he attempts to avoid the skin reaction by employing several ports of entry for the radiation or by other methods, such as that devised by Knox in which the source of radiation works continuously round annular rings of the skin, the dose localised at a depth bearing a greater ratio to the skin dose than by the ordinary method of application.

Auer and Witherbee have experimented on other lines, their aim being to render the skin less susceptible to the rays by inoculation of some reacting substance. Experiments carried out by them upon rabbits make it appear that a previous inoculation of a rabbit with 10 c.cms. of horse serum some days before the X rays were applied rendered the animals less susceptible to the X rays than the rabbit would be normally. The test consisted of finding the dose of X rays which produced a profound disturbance upon the surface of the ear of a rabbit, then delivering this same dose of radiation to animals which had previously received the injection of horse serum.

No doubt the authors will extend the observations to the other tissues of the animal to see whether the protective effect is a general one or restricted to that of the skin. If the latter should prove to be the case, the application of the principle in surface therapy is obvious.

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CHAPTER VII

BLOOD

RADIUM.

We have seen that if the emanation is breathed it goes into solution in the circulating blood, and in this way becomes distributed throughout the body. As a result of the radiation emitted by it and by the active deposit which it is constantly producing, changes in the blood are to be anticipated if the emanation is sufficiently concentrated.

Some observations upon the blood of patients submitted for some hours to an atmosphere containing emanation were made by v. Noorden and Falta, who showed that an increase in the number of white cells occurred, and that this increase was sometimes followed by a decrease.

A more detailed examination of the blood change in dogs and rabbits, when given subcutaneous injections of a soluble radium salt, were subsequently made by Brill and Zehner. A few examples are selected from the very detailed observations they made, which consisted of numerous blood counts at various intervals before and after the injection of the radium.

As a result of such observations they state that after the first rapid rise in the number of red cells there is a further important increase, and this may reach as high as 13,000,000 per cubic mm. The increase is a function of the amount of radium per kilogram weight of the animal. Pathological forms of blood cells were not met with.

In a summary of their work they state that on the leucocyte system there was in all cases a strong stimulation, but with strong doses there is also a harmful effect. Upon the red cell

TABLE 46.

CASE 1. DOG. WEIGHT, 9 KILOGRAMS.

	Days	No. of Red Corpuscles per cubic mm.	No. of Leucocytes per cubic mm.
	1	5,000,000	8,800
	2	—	9,200
	3	—	8,800
	4	—	8,000
	5	—	8,600
	6	—	8,200
	8	5,000,000	8,900
Injection of .0184 mgm. radium in the form of chloride	9	—	12,500
	10	—	14,000
	11	—	18,000
	12	—	19,200
	13	—	23,000
	14	—	25,200
	15	—	16,000
	16	—	16,000
	17	—	24,000
	22	7,000,000	18,000
	36	6,000,000	14,000
	65	6,700,000	10,000

CASE 2. DOG. WEIGHT, 5 KILOGRAMS.

	Days.	No. of Red Corpuscles per cubic mm.	No. of Leucocytes per cubic mm.
	1	5,600,000	12,000
	2	5,300,000	12,400
	3	5,400,000	12,000
Injection of .064 mgm. radium as chloride	½ hour after	7,200,000	16,000
	2 hours after	7,400,000	20,000
	4 " "	—	21,000
	5 days	6,400,000	18,000
	15 "	9,000,000	10,200
	25 "	7,400,000	24,000

TABLE 46—*continued.*

CASE 3. RABBIT. WEIGHT, 3 KILOGRAMS.

	Days	No of Red Corpuscles per cubic mm.	No. of Leucocytes per cubic mm
	1	7,200,000	10,800
Injection of .0042 mgm. radium as chloride	2 hours after	8,100,000	15,200
	5 days	7,600,000	25,000
	15 „	7,800,000	14,000
	25 „	7,000,000	7,800

system they only observed a stimulating effect, which in many cases lasted a long time. These same authors, by frequent examination of the fæces, found that a very large proportion of the soluble radium salt injected remained in the body for some weeks.

If radium emanation be dissolved in physiological saline and inoculated subcutaneously, it becomes distributed throughout the body, and its elimination gradually proceeds via the lungs and the kidneys. Under such circumstances it might be anticipated that comparatively large doses of the emanation could be injected subcutaneously without any very marked changes occurring in the blood. This has been shown to be the case, for some unpublished data of Price-Jones show that as much as 20 c.c. of physiological saline, containing 5 milli-curies per c.cm., could be injected subcutaneously into rabbits without any substantial changes occurring in their blood.

Some of the earliest observations of the effect of the rays upon blood constituents were made by Henri and Mayer, who exposed the blood of the frog and of the dog to 100 mgm. of radium; the exact conditions of exposure, however, are not specified. They observed hæmolysis and the formation of met-hæmoglobin.

Chambers and Russ showed that the red cells of human blood are hæmolysed much more easily by the alpha rays than by the beta and gamma rays; in fact, no hæmolysis was observed with quantities very much larger than the ionising effects of these rays would have indicated as being sufficiently large to produce hæmolysis. Exposure of citrated blood to a concentration of

·52 milli-curie per c.cm. resulted in almost complete hæmolysis after 48 hours.

The leucocytes of the blood are also affected by exposure to the emanation. The same authors measured the phagocytic power of the leucocytes in a specimen of blood, and then at various times after exposure to a concentration of 1.6 milli-curies per c.c. had begun. The following results were obtained :

TABLE 47.

Time of Exposure.	Percentage of Control Phagocytosis.
3 hours 0 min.	93
4 „ 45 „	77
7 „ 5 „	61
8 „ 0 „	46

Prolonged exposure leads to the complete disintegration of the leucocytes.

With regard to other constituents of the blood, they found that the specific properties of opsonin and hæmolytic complement are lost when serum is exposed to alpha rays. The quantitative manner in which these properties diminished under the same intensity of irradiation indicated a separate identity for these two bodies.

There is a lowering of the viscosity of the serum under such intensities of the emanation as have been detailed above. An effect of this kind upon the blood has been recorded by von den Velden, but the concentration of the emanation must have been several thousands of times as small as in the case of the serum to which reference has been made.

Blood changes occurring in man as a result of therapeutic exposures to radium have been recorded, but they do not appear to be uniform ; this is perhaps due to the fact that the majority of radium applications are local rather than general in character, and the regions of the body where radium is applied may be such as to give rise to widely differing blood changes.

In cases where a large portion of the body is irradiated some approach to uniformity in the blood changes might be anticipated, and Lazarus-Barlow records that in 12 out of 20 cases of patients

submitted to a large dose of gamma rays an appreciable diminution in the leucocytes and red cells was observed two days after irradiation.

The reaction of the bone-marrow of rabbits when exposed for prolonged periods to the gamma rays from a large quantity of radium has been studied in some detail by Price-Jones. The animals were exposed for periods ranging from 16-48 hours to the gamma rays from about 5 grams of radium bromide; they were then killed at various times and microscopic examination made of the condition of the bone-marrow of the femur. Very pronounced effects were observed in practically all of the animals examined, the general condition of the bone-marrow being far from normal. The effects upon the different varieties of cells will be found in Table 48. The dominant changes were a combination of white cell destruction, diminished or inhibited formation of granular leucocytes, together with an exaggerated red cell production, this last being a response to the numerous hæmorrhages and the phagocytosis of red cells which occurred in all of the animals.

Cramer, Drew and Mottram have examined the behaviour of blood-platelets of the rat when the animal is exposed to the action of gamma rays. From some preliminary observations they found that, when rats were exposed continuously to the gamma rays from a source of radium, a lymphopœnia occurred within a few hours, a polymorpho-leucopænia in 7 days, and an anæmia in 13 days, death occurring some days later; post-mortem findings proved the existence of a generalised infection with micro-organisms accompanied by a broncho-pneumonia or an enteritis. If the exposures were not continued for so long a time, the anæmia supervened at a later period, and in every instance in which the anæmia occurred the animal died within a few days. This led the authors to the view that the anæmia was not directly due to the radiation but that it was a secondary effect, possibly due to the invasion of the blood stream by organisms. At this stage they endeavoured to link up the behaviour of the animal under radiation with the phenomena observed when it is fed on a diet from which vitamin A is absent. In the latter case the platelets show progressive diminution in their numbers, and this proceeds *pari passu* with the decline in the general condition of the animal, the animals in many cases developing infective conditions.

TABLE 48.

	Single exposure for 16 hours (Combined pairs of Rabbits.)						Three exposures for 16 hours on 3 successive nights (Combined pairs of Rabbits.)	
	Normal	Immediately after $\frac{R_4+R_5}{2}$	3 days. $\frac{R_6+R_7}{2}$	5 days. $\frac{R_2+R_3}{2}$	9 days. $\frac{R_8+R_9}{2}$	16 days $\frac{R_{13}+R_{14}}{2}$	Immediately after. $\frac{R_{10}+R_{11}}{2}$	7 days $\frac{R_{12}+R_{15}}{2}$
	%	%	%	%	%	%	%	%
Primitive cells - -	29.5	21.3	23.1	38.7	40.4	28.0	19.3	42.3
Myeloblasts - - -	15.5	16.1	32.3	19.7	40.4	41.4	16.9	37.1
Giant cells - - -	0.9	2.8	3.5	1.1	4.2	2.0	8.0	4.9
Other lymphoid cells -	3.7	3.2	3.3	3.9	7.5	8.9	10.3	12.9
Total lymphoid cells -	49.6	43.4	62.3	63.5	92.5	80.4	54.6	97.2
Granular myelocytes -	45.8	48.1	34.8	33.7	7.0	16.5	39.3	2.6
Polymorph leucocytes -	4.6	8.4	2.8	2.7	0 4	3.0	6.0	0.1
Total granular cells -	50.4	56.5	37.2	36 4	7.4	19.5	45 4	2 7
Megaloblasts and metrocytes	3.0	8.1	15.4	17.4	46.0	39.7	0.9	38.7
Normoblasts - -	6.5	31.7	20.8	21.9	135.1	50.7	8.3	69.3
Free nuclei - - -	6.2	7.6	9.7	6.8	34.9	18.8	8.7	55.7
Total nucleated red cells per 100 white cells	15.7	47.4	45.9	46.1	216.3	109.2	17.9	163.8

The effect of the gamma rays upon the blood-platelets was to cause a rapid diminution in their numbers followed by a rapid recovery; this was the case for an exposure of limited duration and one which produced no effect whatever upon the red cell and hæmoglobin content. With more prolonged exposures there is no recovery on the part of the animals to the normal platelet content, and they die from intercurrent infections.

These experiments are of a highly suggestive character, for if the authors' interpretation is correct, they show how some change of a simple character set up in the body by means of radiation can give rise to other changes of a nature sufficiently grave to cause death.

The effect of exposure of people to very small doses of gamma rays over long periods of time has been investigated by Mottram, who showed that such exposures gave rise to profound changes in the blood; practically every type of blood cell being affected. This finding is an additional warning to radiologists of the necessity for precautions against the harmful effects of the radiations they employ.

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X RAYS. BLOOD CHANGES. (IN VIVO.)

Attention was first directed by Senn in 1903 to the effect of X rays upon the spleen in cases of leukæmia, and the inference that important changes occur in the blood as the result of such irradiation gave an impulse to experimental work in this direction.

Profound changes occur in an animal, such as a rat, rabbit, guinea-pig or dog, when exposed to X rays; with a sufficiently long exposure death may quickly ensue.

Numerous investigators have examined the blood of such animals before and during the irradiation, and although they are agreed that important changes do occur in the constitution of the blood, the precise nature and extent of such changes are not yet known.

Helber and Linser, soon after the pioneer work of Heineke on the effect of X rays on various animal tissues, exposed rats, rabbits and dogs in a similar manner, with a view to detecting changes in the blood.

The outstanding feature of their work was to show that a diminution in the total number of white cells is the general effect of prolonged exposure to X rays. They state that in the case of rats irradiated for 5–10 hours the blood may become entirely free of leucocytes, and that this may also happen with rabbits and dogs if the exposure be long enough. The lymphocytes appear to be the most sensitive of the white cells to the rays, the red cells being much less affected.

The following data in Table 49, due to Helber and Linser, show in a general way the type of blood changes obtained upon irradiation of a rabbit.

TABLE 49.—GREY RABBIT.

Date.	Weight.	X rays. Hours.	Number per cubic mm.			Percentages.		Absolute numbers per cubic c.mm.	
			Red cells.	Haemoglobin.	White cells.	Lymphocytes.	Polynuclear leucocytes.	Lymphocytes	Polynuclear leucocytes.
10/12	2,400 gms.	0	7,700,000	80	6,500	32	62	2,080	4,025
11/ ,,		6	6,820,000	80	7,500	14	83	1,050	6,240
12/ ,,		0	7,530,000	70	7,500	8	89	600	6,680
16/ ,,	2,200 ,,	4	5,960,000	60	7,000	8	89	560	6,240
17/ ,,		5	5,400,000	60	6,000	8	88	480	5,280
18/ ,,	2,000 ,,	17	5,490,000	50	2,500	6	92	150	2,300
19/ ,,		13	6,115,000	60	2,000	6	84	120	1,680
21/ ,,		17	4,610,000	50	1,400	6	36	84	504
24/ ,,	1,800 ,,	16	4,520,000	55					

Helber and Linser stated, as a result of their work, that leukotoxins are formed in the blood of an animal when irradiated, and that such leukotoxins can be transferred from one animal to another.

Most other authors have not been able to substantiate this claim. While Kleinberger and Zoeppritz (in 1905), Milchner and Wolff (in 1906), and Tatarsky (in 1907) have not been able to find satisfactory evidence of such leukotoxins, they are in accord with Helber and Linser as to the greater effect X rays have upon lymphocytes than upon any other constituents of the blood.

A series of investigations upon the changes of the blood of rabbits due to exposure to X rays was made in 1906 by Benjamin, Reuss, Sleuka and Schwartz. These authors showed the susceptibility of the lymphocytes to these rays and the initial increase in the polymorpho-nuclear leucocytes that often results from an exposure to the X rays. With reference to the gradual disappearance of lymphocytes from the blood, the question arises as to whether they are destroyed in the circulation or as a result of some action of the rays upon the hæmopoietic organs. These authors performed the following experiment to show that destruction of the lymphocytes in the blood stream does occur : a rabbit was protected from the rays with the exception of its ears, which were irradiated for 170 hours, the time of irradiation being prolonged to compensate for the small surface irradiated. The general trend of the blood changes subsequently observed was the same as when the whole animal was irradiated, an important difference, however, being that the effect was of a very temporary nature, the blood returning to a normal condition 24 hours after the exposure was stopped, whereas 7–10 days are necessary when the animal is irradiated " in toto."

These authors attempted to detect the products of decomposition of the lymphocytes in the circulating blood, and state that the presence of choline could be demonstrated some hours after irradiation had begun. No proof, however, is given by them that the quantitative production of this substance runs parallel with the observed diminution of the number of lymphocytes in the blood stream.

Tatarsky, in an extensive piece of work upon this subject, discusses the methods by which the lymphocytes of the blood are destroyed by the rays. He considers three possible ways in which

this destruction may take place: (1) The lymph glands and follicles may be specially sensitive to the action of the rays, their function being so interfered with that the production of new cells is hindered or completely stopped. (2) They may be destroyed in the circulating blood, or (3) the normal evolution of the lymphocytes to the polynuclear leucocyte (*sic !*) may be accelerated under the action of the rays, with the result that there is a reduced number of lymphocytes found in the circulating blood. Tatarsky considers the first to be the most probable way in which the X rays act.

Some of Tatarsky's findings are of a striking nature; witness the case of a white rabbit which, as a result of 10 hours' exposure, at various intervals showed the blood changes exhibited in Table 50.

The initial *increase* in the white cells, in spite of the decrease in the number of the lymphocytes, was observed in every case except one. The first mention of such a change occurring as a result of an exposure to X rays is to be found in a paper by Aubertin and Beaujard in the treatment of a patient suffering from leukæmia; but this particular change does not invariably occur when such treatment is resorted to.

TABLE 50.—WHITE RABBIT.

Date.	When examined.	Length of exposure.	Number per cubic mm.		Percentages.		Absolute Nos	
			Red cells.	White cells.	Lymphocytes.	Polynuclear leucocytes.	Lymphocytes.	Polynuclear leucocytes.
19/8/05	Before exposure	—	5,176,000	13,200	64	32	8,450	4,220
	Directly after	3 hours	4,888,000	21,200	18	79	3,820	16,750
21/8/05	Before exposure	—	4,864,000	9,000	29	66	2,610	5,940
	2 hours after	2 hours	—	13,400	—	—	—	—
	Immediately after	2½ ,,	4,896,000	13,100	10	82	1,310	10,750
22/8/05	Before exposure	—	4,720,000	11,100	14	84	1,540	9,340
	½ hour after	2 ,,	—	14,100	—	—	—	—
	1¾ hours after	—	—	42,000	—	—	—	—
	5 hours after	—	—	4,500	—	—	—	—
23/8/05	—	—	5,040,000	1,900	46	42	875	800
24/8/05	—	—	5,040,000	1,700	32	60	544	1,020

Fränkel and Budde made an investigation upon the histological, cytological and serological changes occurring in guinea-pigs when exposed to X rays. Their observations are divided into three groups, according to the dose of X rays used, and some of the most important blood changes are grouped together in Table 51 (Lot 1, Lot 2, Lot 3). Some of the features are rather variable, but in general their findings are analogous to those of Tatarsky, the most interesting feature being the initial rise in the number of leucocytes followed by a leukopænia.

A considerable step towards elucidating the mechanism of the blood changes to be observed in animals subsequent to their exposure to X rays was made by Aubertin and Beaujard in 1908. One of the special features of their work was the administration to their animals (guinea-pigs) of not larger doses of X rays than would be given to a patient suffering from leukæmia ; as they point out, considerable changes occur in the blood of animals when given large doses (4–6 hours' exposure), but the interest

Lot 1.

TABLE 51.

Erythema doses	Blood examined.	Leucocytes. Per cubic mm.	Polynuclears. Per cent.	Mononuclear lymphocytes. Per cent
1				
—	Before radiation	13,700	58	35
4½	At once	28,000	—	—
—	½ hour after	14,200	—	—
—	1 ,, ,,	13,000	—	—
4½	At once	24,750	—	—
—	1 hour after	12,800	—	—
—	2 hours after	13,500	65	29
—	24 ,, ,,	6,000	44	52
—	3 days after	1,300	47	45
—	1 week after	3,200	76	24
2.				
—	Before radiation	10,400	85	14
4½	At once	5,400	56	41
—	1 hour after	3,700	72	25
4½	At once	7,600	87	13
—	1½ hours after	2,600	89	11
—	24 ,, ,,	3,600	77	22

Lot 2. Smaller doses frequently repeated.

	No. of exposures	Total dose.	No of leucocytes per cubic mm.
1	18	8 erythema doses	500
2	16	7·7 ,, ,,	1,050
3	25	12.5 ,, ,,	3,800
4	23	11.5 ,, ,,	4,330

Lot 3. One exposure

	Erythema doses.	Examined after.	No. of leucocytes per cubic mm.
1	2 +	11 days	8,800
2	2	10 ,,	4,800
3	2	10 ,,	2,200
4	2	10 ,,	1,850
5	2	10 ,,	10,800

therein is certainly lessened by the fact that such exposure is generally fatal to the animal in the course of a few days. Another, and perhaps even more important, feature was their attempt to compare the relative importance of the parts played by the spleen and by the bone-marrow in the changes in the blood. This had in some measure been attempted previously by Heineke, who was able to show the much greater susceptibility of the spleen than of the bone-marrow to irradiation.

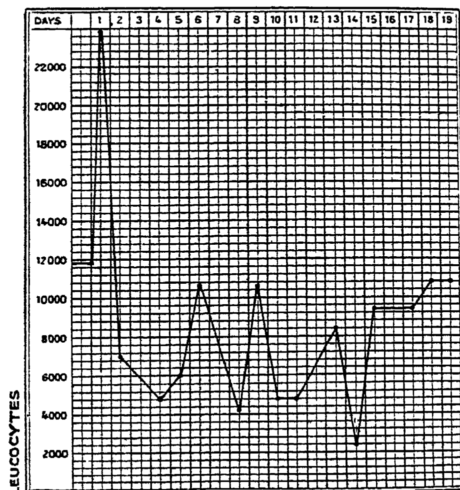


Fig. 29.

The general scheme of the observations of Aubertin and Beaujard was to expose the whole animal to a moderate dose of X rays (12H, 6–7 Benoist), the exposure

lasting 40–60 mins. Frequent examinations of its blood were then made, beginning as soon as 2 hours after the exposure was over; these were continued until a normal condition was reached. A typical case is illustrated in Fig. 29, and the details of the blood-counts are collected in Table 52. The initial feature, namely, a sharp rise followed by a pronounced fall in the number of leucocytes, is as clearly seen as in the cases to be found in the previous pages. The feature to which Aubertin and Beaujard call particular attention, however, is the oscillatory nature of the graph before a normal condition of the blood is reached; they suggest that this indicates a reaction on the part of the animal, tending to restore things to a normal condition. From the detailed blood-counts it is possible to trace the variations of each class of white cell, and in this way determine the relative part they play in the process by which the blood returns to its normal condition.

TABLE 52.

Guinea-pig. X Rays = 12 H.	Total White Cell Count.	Polynuclears.	Degenerate Polynuclears.	Mononuclears.	Degenerate Mononuclears.	Large Mononuclears.	Eosinophiles.	Mast Cells.	Myelo-neutrophiles.	Basophiles.
Before exposure - -	11,800	39 5	—	57	—	1	2	0 5	—	—
2 hours after - -	24,000	67	22	8	1	—	1	—	1	—
2 days (20 hours after) -	7,200	33	18.5	40 5	6	0.5	1	0 5	—	—
3 ,, ,,	—	43	22	23.5	9	0 5	2	—	—	—
4 ,, ,,	4,800	34	12.5	18.5	2	1.5	9 5	2	—	—
5 ,, ,,	6,000	27	24.3	31.3	5	—	8 3	4	—	—
6 ,, ,,	10,800	44	11	31 5	4	—	3 5	6	—	—
7 ,, ,,	—	28.5	19	45	2.5	1 5	2	1 5	—	—
8 ,, ,,	4,200	35	7	45	0 5	2	8	2	0.5	—
9 ,, ,,	10,800	35	7	48	1.5	2	3 5	3	—	—
10 ,, ,,	4,800	23 6	12 3	52	2	2.3	4 6	2 3	—	0 6
11 ,, ,,	4,800	35	12	46	2	1	4	1	—	—
12 ,, ,,	—	60	5	24	5	—	4	2	—	—
13 ,, ,,	8,400	45	6	38	3	—	5	2	—	—
14 ,, ,,	2,400	36	5.5	48.5	2	0 5	6 5	1	—	—
15 ,, ,,	9,600	50.5	5	36.5	2	—	5	1	—	—
17 ,, ,,	9,600	37	3	43	0 5	—	16	0.5	—	—
18 ,, ,,	10,800	32	1	53	1	1 5	10 5	1	—	—
19 ,, ,,	10,800	40	1	50	1	—	8	1	—	—

During the leukopenia, the polynuclear forms generally decrease in number, but not to so great an extent as other

varieties; in fact, they may actually increase beyond their usual percentage, and often consist of immature forms, uni- and bi-nucleated, which is indicative of an accelerated production in the bone-marrow.

A notable increase in the eosinophile and mast cells is, according to these authors, further evidence of a state of hyper-activity in the bone-marrow. That this condition of hyper-activity, together with a reduced activity of the spleen, partly accounts for the variations observed is possibly the case, and this view is borne out by their observations upon the spleen and bone-marrow of the animals at varying periods subsequent to their irradiation.

From their systematic observations on the spleen, they found that in animals killed 40 hours after being irradiated the condition of necrosis in the follicles, to be seen up to this time, had disappeared, and the Malpighian corpuscles were completely regenerated; in view of the fact that the leucopenia often progressed considerably beyond this period, they suggest that the reduction in the number of lymphocytes cannot be caused by the destruction of lymphopoietic tissue. In the spleen pulp, the repeated finding of macrophages and of leucocytic débris during the period of the leucopenia was the outstanding feature. The bone-marrow over this same period was in a condition of manifest hyper-activity; the main evidence for which was (1) Increase in the number of granular myelocytes and mother-cells having basophile protoplasm. (2) Increase in the normal proportion of polynuclear and of transition forms of white cells. (3) Increase in the normal proportion of eosinophile and mast cells.

As a general conclusion to these observations upon the marrow, they state that: " A medium dose of X rays causes a condition of hyper-activity of the bone-marrow which, though apparently paradoxical, is the more accentuated the more marked the decrease in the leucocyte content of the blood; this condition does not disappear until the blood content is normal." Such a conclusion carries with it another to the effect that the bone-marrow is much less sensitive to irradiation than is the spleen. It is, of course, difficult to be quite certain that under the experimental conditions both organs received and absorbed the same dose of X rays; nevertheless, it may be held that under the same exposure they react in a totally different way.

The problem as to how the changes are actually produced in

the blood of an animal after exposure to X rays is indeed a complex one. When we consider that, besides the circulatory system, the spleen, the lymphatics and bone-marrow all play an important part in deciding what the blood-count is to show at any subsequent time, it is no matter for surprise that unanimity is not yet reached on the question of mechanism. The main facts to be gleaned from the experimental work which has been considered are that, subsequent to even moderate doses of X rays, the leucocytes show an initial rise in numbers followed by a pronounced fall, but this is followed by a rise to the normal figure; as regards the erythrocytes, there is an initial fall, which may last for long periods or be made good in the course of a few days. The conclusions of Aubertin and Beaujard would lead one to believe that the destruction of the leucocytes occurs in the blood stream, that the diminution in the number of lymphocytes is due to this action as well as to inhibitory processes in the spleen, and that these influences more than counterbalance the enhanced output of the bone-marrow. The work of Price-Jones has shown that when the erythrocytes are destroyed to any extent in the circulation, the response of the organism is an enhanced activity of the bone-marrow, and in view of the fact that such a destruction is a constant feature after exposure to X rays, it is worth considering what part this may play in the augmented activity of the bone-marrow, although Aubertin and Beaujard leave one to assume that it is a direct result of the irradiation. Their repeated exhibition of the oscillatory nature of the return of the blood to a normal leucocytic content is of great interest, and it is just in the consideration of such complexity of process that the meagreness of any attempted explanation of it is apparent. If the stimulation of the bone-marrow is sufficient (*vide* Fig. 29, 6th and 9th days) to restore the blood of the irradiated animal practically to its normal leucocyte content, the question arises as to why it is not kept there. If there is a destruction of leucocytes in the circulation and in the spleen, the origin of the initial rise in their numbers, which is almost invariably the sequel to an exposure, remains unexplained. These are but some of the more obvious difficulties that prevent one stating that an adequate explanation of the mechanism of the blood-changes induced by X rays is before us.

Murphy and his colleagues at the Rockefeller Institute have,

since 1915, carried out a large number of important observations upon the effects of exposing animals, such as rats, guinea-pigs and dogs to X rays of varying character and intensity. It is impossible even to summarise the results of these investigations here, but they show both the destructive and the stimulative effects of the rays upon the blood elements. Especial interest centres round these studies upon lymphocytic activity, for previous researches of Murphy had indicated that some close relationship seemed to exist between the lymphocytic activity of an animal and the mode of growth of a tumour when inoculated into it. If, for instance, a tumour is removed from the animal and examined microscopically, it is seen to be the seat of great lymphocytic activity; again, if a rat be immunised towards a tumour and then re-inoculated with the tumour, the small grafts which result from this are found to be surrounded by lymphocytes and plasma cells. While it is true to say that the immune condition in these animals is, in many instances, associated with a lymphocytic activity, we are equally on safe ground in stating that a large increase in numbers of these circulating lymphocytes does not bring about the immune condition, as the following experiment will show.

During some experimental studies upon the effect of comparatively small doses of X rays upon the circulating lymphocytes of the rat, Russ, Chambers, Scott and Mottram showed that the usual sequel to exposing a rat to X rays is a temporary disappearance from the circulation of a considerable proportion of the lymphocytes. If the exposure be repeated at intervals of a fortnight the same temporary effect is noted, but as time goes on the numbers of lymphocytes in the animal may be largely increased, in some cases to four or five times the original figure. A test of the susceptibility of such animals towards Jensen's rat sarcoma showed that they differed in no important particular from the rat having a normal lymphocytic content.

It looks, therefore, as though lymphocytic activity is only one, but possibly a very important, aspect of the immune condition, and that other processes are involved, and indeed essential, before this lymphocytic activity can function in a capacity detrimental to tumour growth.

It is interesting to find that rays which have very small power of penetrating the tissues can yet affect the blood of an animal exposed to them; this has been shown for X rays of long wave-

length by Murphy and Morton, and by Taylor and Witherbee, for beta rays of equivalent penetrating power by Mottram and Russ and for ultra-violet rays by Riedel and others.

It is not a little remarkable that ultra-violet radiation which is capable of penetrating through only a very thin layer of skin can give rise to important blood changes in individuals submitted for very prolonged periods to it.

Concerning changes in the blood other than in the different varieties of cells, little that is definite is known. Reference has already been made to the possibility of leukotoxins being formed, but the evidence that this actually occurs is not convincing.

Fränkel and Budde, in their experiments upon guinea-pigs (*vide supra*), showed that in some cases the amount of hæmolytic complement was diminished subsequent to irradiation ; but the effect was not a constant feature nor was it proportional to the extent to which the animal was irradiated.

Fiorini and Zironi submitted rabbits to doses of 10–12X without detecting any difference in the hæmolytic power of their blood when compared with that of normal rabbits.

Changes occur in the blood of man as a result of chronic exposure to X rays. Aubertin has chronicled the result of blood examinations upon seven radiologists who were in good health, and did not suffer from any lesions. He states that the blood of these radiologists was not quite normal, the most marked feature being a diminution in the number of red cells. Table 53 gives the data corresponding to the cases cited above.

TABLE 53.

	Age.	Period X rays were used.	Number per cubic mm		Poly-nu-clear.	Mono-nu-clear.	Lym-pho-cytes.	Eosino-phile.	Large Mono-nu-clears.
			Red cells.	White cells.					
(1)					Per cent.	Per cent.	Per cent.	Per cent.	Per cent
I.	31	9 years	4,340,000	4,000	74	12	2.5	5	6.5
II.	37	8 ,,	4,040,000	6,400	76	14.5	3.5	3	3
III.	36	7 ,,	4,760,000	8,000	81.5	10	4	2.5	2
(2)									Giant cells.
IV.	39	10 ,,	3,940,000	10,800	67	10	4	7	11
V.	35	6 ,,	—	—	59	21.5	5	5.5	9
(3)									
VI.	40	11 ,,	4,200,000	4,800	45.5	39.5	6.5	2.5	6
VII.	33	6 ,,	4,540,000	6,400	57	16.5	15 (5 large)	1.5	10

The initial discovery of Senn that X rays have a beneficial effect upon the blood in cases of leukæmia has had a very extensive application in radio-therapy, and the literature dealing with such cases is a very extensive one. The gradual effect upon the pathological condition of the blood in leukæmia is well shown in the records of two cases of spleno-medullary leukæmia cited by Ironside Bruce, from which the data in Table 54 are selected to illustrate the outstanding effects upon the red and white corpuscles.

TABLE 54.

Case 1. Daily doses of X rays extending over a period of about 6 months, with the exception of two intervals of a fortnight.

	Red cells.	White cells.		Red cells.	White cells
July 26	3,047,000	400,000	Oct. 12	4,696,000	226,000
Aug. 2	3,085,000	461,000	„ 27	3,975,000	117,000
„ 13	3,150,000	499,000	Nov. 9	4,550,000	72,000
Sept. 6	3,200,000	426,000	Dec. 8	4,550,000	32,000
„ 16	3,810,000	290,625			

Case 2. Very frequent application of X rays extending over a period of a year.

	Red cells.	White cells.		Red cells.	White cells
Sept. 10	2,300,000	1,440,000	Feb. 21	4,750,000	42,000
„ 30	2,360,000	1,110,000	Ap. 4	4,280,000	97,000
Oct. 28	3,020,000	232,000	July 14	4,040,000	183,000
Jan. 6	3,842,000	96,000	Sept. 9	4,170,000	202,000

A detailed study of the action of X rays upon a case of spleno-medullary leukæmia was made by Ledingham, who endeavoured to correlate the blood changes observed during treatment with the changes subsequently found in the spleen, lymph glands, marrow and liver. The bone-marrow was found to be in a markedly hypoplastic condition, but the most conspicuous features were exhibited by the spleen; the neutrophile elements usually associated with the condition were found to be almost entirely replaced by undifferentiated basophile myelocytes in a proliferating condition. Ledingham, however, remarks upon the

difficulty of bringing the general clinical signs into relationship with the blood changes; he also advocates great caution in continuing X-ray treatment once the total leucocytes have attained normal limits

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X RAYS. BLOOD (IN VITRO).

Bergonié and Tribondeau submitted defibrinated blood to the action of X rays for periods up to half an hour, the distance from the anti-cathode being from 10–15 cm.; they were not able to detect any free hæmoglobin or other changes.

Fiorini and Zironi exposed the serum of guinea-pigs in glass dishes to X rays (5–10X) at a distance of 10 cm. from the anode. No certain action was obtained upon the immune body or upon the complement contained in such serum.

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CHAPTER VIII

BLOOD-VESSELS

RADIUM.

IN 1903 Halkin, in the course of his investigations upon the action of radium on the skin, observed degenerative changes in the walls of the blood-vessels of the irradiated part. He employed 0.13 gram of radium-barium bromide, enclosed in a metal capsule with an aluminium cover .1 mm. in thickness. The animals used were young pigs, and the exposure was for one hour. At the expiration of twenty-four hours no deviation from the normal was detected; but after three days, the capillaries, on microscopical examination, were seen to be more distinct. After five days there was some definite distension of the vessels, but no perivascular infiltration. On the seventh day, diapedesis was seen to have occurred, but only to a very small extent. The whole capillary network and the small vessels showed marked dilatation, and were distended with blood. The endothelial cells were swollen, and their nuclei enlarged. On the twelfth day, the degenerative changes were still more marked. The vessels and capillaries, still dilated and engorged, showed marked changes in their walls, which in the case of the vessels were rumpled and laminated, while the endothelial cells in all cases showed vacuolation. On the twenty-fourth day, the degeneration had progressed to such an extent that in many places the capillaries formed wide blood spaces, whence hæmorrhages occurred into the tissues.

Halkin does not regard this series of changes as a mere inflammation phenomenon, since diapedesis, when it occurs, is remarkably small in amount and late in appearance; he thinks that they

are rather to be attributed to loss of tone and resistance of the cell wall, whose degeneration is clearly shown by the vacuolation of the protoplasm of the endothelial cells.

Danysz in 1903 noticed hæmorrhages in the brain and spinal cord of mice when exposed to radium, a result which has been confirmed by numerous other observers.

Thies (1905) exposed the skin of guinea-pigs to 20 mgr. of radium bromide for six hours. In this case dilatation and distension of the vessels were noted after twenty-four hours, while

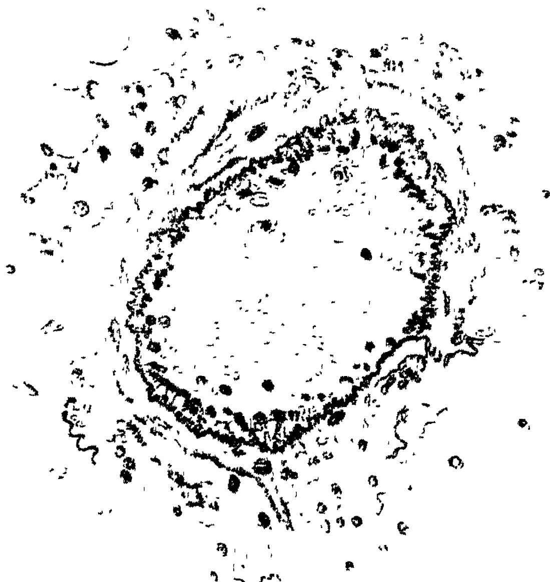


FIG. 30—Artery of guinea-pig 14 days after an exposure of 24 hours to 10 mgms. of radium bromide placed .5 cm distant

after three days the endothelial cells were swollen, and in many places the vessel walls infiltrated with leucocytes. On the eleventh day the changes had progressed: the endothelial cells were much more swollen, the middle coat of the arteries showing still further infiltration, while the differentiation of individual cells and nuclei was rendered obscure. These alterations are well exhibited in Fig. 30. The changes in the veins were not so marked. The capillaries were greatly engorged, but their walls severely damaged, and numerous capillary hæmorrhages were observed. By exposing the vessels themselves directly to

the radium capsule, Thies found that the veins suffered more extensively than the arteries.

Obersteiner (1905) described fatty changes in the endothelium of blood-vessels as a result of exposure to radium, and Horowitz (1911) confirms the degenerative changes in the endothelium, and the infiltration of the coats of the vessels by leucocytes.

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CHAPTER IX

SPLEEN

RADIUM.

THIES, in his investigation of the action of radium upon the spleen of the guinea-pig, exposed the organ for six hours, when the radium (20 mgms.) was removed, and the wound closed. At the expiration of thirty-six hours, marked changes were noticed. The site of irradiation was distinguished by a bright red spot upon the surface of the organ, the lymph follicles were indistinguishable, or very small, while in the spleen pulp were free red-blood corpuscles and pigment granules. Eosinophile cells were also occasionally to be seen in the pulp, but the connective tissue and the capsule of the spleen were unaltered. On the third day more marked congestion was noted, and the eosinophile cells had increased in number. On the fourteenth day the whole organ had undergone diminution in size; the follicles were now distinct and of normal size, but somewhat diminished in number. The cellular elements of the pulp were normal, and the number of eosinophile cells was small.

The most marked splenic changes observed by Thies occurred in white mice which had been irradiated *in toto*. After a four to five days' exposure, lymphocytes were still present in fair numbers, though less than normally. If the exposures were longer (10–11 days), practically no lymphocytes were to be seen. Small pigment masses were found, especially around the arteries, but also in other parts of the spleen pulp. The connective tissue was increased in amount. In the blood there was a marked diminution of white cells, very few polymorphonuclear cells, and hardly ever any mononuclears. In addition, the lymphatic glands and solitary lymph follicles were free from lymphocytes. Side by side with these changes in the spleen there were changes

in the bone-marrow (9–11 days' exposure). There was an almost complete disappearance of cellular elements, and only an occasional polymorphonuclear or mononuclear cell could be seen. In other cases the marrow cavity was filled with red-blood cells, and hæmorrhages were numerous. Horowitz also bears witness to the extreme sensitiveness of the spleen bone-marrow and lymphatic system towards radium.

Heineke has recently shown (1913) that profound changes may be produced in the spleen and intestinal lymph follicles of rabbits and guinea-pigs by irradiation of very short duration. For this purpose he employed an ebonite capsule containing 20 mgr. of radium bromide covered by a thin mica plate, and enclosed the whole in a rubber finger stall. The organ was exposed, by an abdominal incision, and the radium, protected as described, applied to its surface. Even a five seconds' exposure was sufficient to produce marked destruction of the cell nuclei; it may be noted that irradiation of the skin for the same period produced no change whatever. Upon irradiating the surface of the abdominal wall for one hour, a marked destruction of the lymphocytes in the abdomen was produced, and the interposition of 3 mm. of lead between the radium and the skin had but comparatively little effect upon this destructive action.

It is a well-known fact that the spleen plays an important part in certain conditions of leukæmia, and irradiation of the organ is often attended by the onset of favourable symptoms. A case cited by Rénon, Degrais and Thibaut is of particular interest in this connection, for they observed what may be called typical blood changes in a case of myeloid leukæmia when exposed to the rays from radium, in spite of the fact that the spleen had previously been removed. The data are of such interest that they are given in detail: the spleen, weighing 2.8 kilograms, was removed on Feb. 1st, 1913, the leucocytes fell from 220,000 to 27,500, which was followed by a rise in their numbers, and the subsequent procedure was as follows:

25th March. Red cells, 2,520,000. White cells, 70,500.

Mononuclears - - - - -	18 per cent.
Large mononuclears and neutrophile myelocytes	31 „
Neutrophile polynuclears - - - -	49 „
Eosinophile myelocytes - - - -	1 „
Nucleated red cells - - - - - -	7 „

Benzole treatment, 18 drops per day for one month. Blood examined every eight days.

5th April. Red cells, 2,120,000. White cells, 116,500.

Large mononuclears and neutrophile myelocytes - - - - - - -	62 per cent
Neutrophile polynuclears - - - - -	37 ,,
Eosinophile myelocytes - - - - -	1 ,,
Nucleated red cells - - - - - -	5 ,,

12th April. Red cells, 2,450,000. White cells, 143,500.

Large mononuclears and neutrophile myelocytes - - - - - - -	91 per cent
Neutrophile polynuclears - - - - -	8 ,,
Eosinophile myelocytes - - - - -	1 ,,
Nucleated red cells - - - - - -	5 ,,

Splenic region treated with radium; application of 330 mgms. Radium Sulphate for 24 hours, screened by 2 mms. of lead, active material spread over an area of 600 sq. cms.

19th April. Red cells, 2,770,000. White cells, 119,000.

Large mononuclear and neutrophile myelocytes - - - - - - -	64 per cent
Neutrophile polynuclears - - - - -	34 ,,
Mononuclears - - - - - - -	1 ,,
Eosinophile myelocytes - - - - -	1 ,,
Nucleated red cells - - - - - -	2 ,,

20th April. Second application.

26th April. Red cells, 2,610,000. White cells, 30,500.

Large mononuclear and neutrophile myelocytes - - - - - - -	45 per cent.
Neutrophile polynuclears - - - - -	51 ,,
Mononuclears - - - - - - -	3 ,,
Eosinophile myelocytes - - - - -	1 ,,
Nucleated red cells - - - - - -	7 ,,

27th April. Third application.

30th April. Red cells, 2,540,000. White cells, 21,500.

Large mononuclear and neutrophile myelocytes - - - - - - -	16 per cent.
Neutrophile polynuclears - - - - -	55 ,,
Mononuclears - - - - - - -	29 ,,
Eosinophile myelocytes - - - - -	1 ,,
Nucleated red cells - - - - - -	9 ,,

3rd May. Red cells, 3,020,000. White cells, 25,500.

Large mononuclear and neutrophile myelocytes - - - - - - -	19 per cent.
Neutrophile polynuclears - - - - -	62 ,,
Mononuclears - - - - - - -	21 ,,
Eosinophile myelocytes - - - -	1.5 ,,
Nucleated red cells - - - - - -	·5 ,,

It will be observed that the changes in the blood are of an identical character to those found in cases where a hypertrophied spleen has been irradiated. The observation is a very significant one.

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SPLEEN (X RAYS).

The first systematic attempt at finding the nature of the changes set up in the internal organs of animals subjected to X rays was made by Heineke, who in 1905 published the details of his investigations upon mice, guinea-pigs, rabbits and dogs. These animals were given massive doses of X rays, doses in fact large enough to ensure their death in a few days or weeks, and the subsequent changes (macro- and microscopic) induced in various organs were observed and described by Heineke. As some of the most striking changes were exhibited by the spleen, it is appropriate that these investigations of Heineke be considered in this section, although his observations were by no means restricted to this organ. It is well to recognise in connection with these observations that the effects are as a rule to be associated with the administration of very large doses of X rays, and it is necessary to bear in mind that whereas if a healthy organ be given a small dose of X rays, the condition of the organ does not appreciably change during such an irradiation, it is far otherwise when the organ is subjected to prolonged exposure, for appreciable changes take place during the first part of the exposure, rendering the organ a pathological, rather than a normal, one for the remainder of the irradiation.

Heineke's procedure was generally to expose the animal to the unscreened X rays from a bulb 15–20 cms. distant for several hours at a time, the procedure being repeated at various intervals. He summarises the macroscopical effects observed in mice, young guinea-pigs and rabbits in the following way :

1. Mice and young guinea-pigs and rabbits are killed by exposing them for several hours to X rays, death ensuing about 8 days after the exposure ; apart from a loss of hair and tenderness, the skin shows no lesion during this time.

2. Adult guinea-pigs and rabbits also die after exposure to X rays, but rather as a sequel to lesions set up in the skin.

The corresponding microscopical observations Heineke summarises thus :

I. In the above animals which, at the time of death, show no visible changes in the skin, microscopical examination revealed small changes, which were more pronounced with the larger doses. In mice alone was evidence lacking of any trace of Röntgen-dermatitis.

II. Without exception, changes were observed in the internal organs of the animals succumbing to the X-ray exposures ; they were :

(*a*) Changes in the spleen, which were of a twofold character :

(1) Cellular destruction, especially of the lymphocytes in the follicles and spleen pulp.

(2) Diminution of pigment very marked in mice, less so in guinea-pigs and rabbits.

(*b*) Changes in the lymph glands, consisting in the destruction of the greater part of the lymphocytes in and around the follicles.

(*c*) Changes of a similar character in the follicles of the intestine.

(*d*) Changes in the bone-marrow, consisting of an extensive rarefaction of certain cells.

Discussing the cause of death of the animals, Heineke gives reasons for believing that it is not due to any one particular change induced by the rays. The nervous system appears to be singularly unaffected, the blood changes are inadequate of themselves to cause death, the changes induced in the skin are often hardly discernible in young animals succumbing about a week after exposure, and the effects described in Section 2 above were shown by Heineke not to be necessarily associated with a fatal sequel ; it appears likely therefore that death is the result

of a large number of contributory causes rather than of any specific one.

The changes in the blood-producing organs were the earliest recognisable, and were found to fall into two groups: changes in the lymphoid tissue of the spleen, lymph glands, and intestinal follicles; and changes in the bone-marrow and spleen pulp. The former appear within a few hours ($2\frac{1}{2}$–3) of irradiation, and

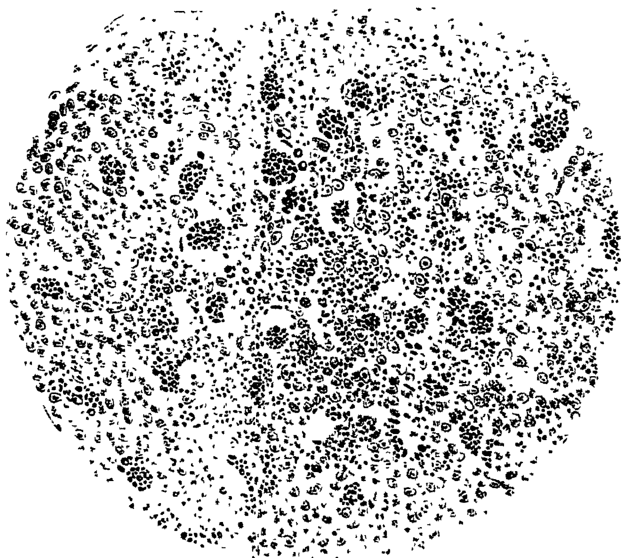


FIG 31.—Guinea-pig exposed to X rays for 5 hours, then killed.
Section through spleen follicle. In the centre of the follicle large quantities of free nuclear fragments and numerous phagocytes.

Mitteilung aus den Grenzgebieten der Medizin u. Chirurgie (14), 1905.

are complete in about 24–36 hours; the latter are only recognisable after the lapse of a few days, and increase in intensity till the death of the animal occurs.

The first effect of the radiation is the destruction of lymphoid tissue in every region of the body; this process appears to be quite independent of the subsequent cell destruction that occurs in the spleen pulp and bone-marrow.

The rapidity with which the changes in the lymphoid tissue occur render it most probable that the effect is indeed a direct one, and that this particular kind of cell is among the most

vulnerable to the X rays. Heineke was of the opinion that they were of all cells the most vulnerable ; but it is a question whether this might not be said of certain of the cells of the testicle, or of some varieties of new growths.

The various stages in the destruction of lymphoid tissue were studied by Heineke in detail, and the sequence of events may be briefly indicated as follows. In the first two hours of irradiation no histological changes are recognisable, but shortly afterwards (2½–3 hours) the nuclei of the lymphocytes suddenly disappear, and there is a liberation of chromatin, which then



FIG 32—Cat exposed to X rays for 5 hours, killed four hours later.
Section through the intestinal follicle. A great reduction in the number of lymphocytes, between which are numerous spheres of chromatin.
Mitteilung aus den Grenzgebieten der Medizin u. Chirurgie (14), 1905.

collects into a number of small spheres—this action appears to start in the more central parts of the spleen, and to proceed gradually to the peripheral portions ; with the onset of destruction of the lymphocytes, phagocytes make their appearance and gradually clear the tissue of the disintegrated cells. During this process certain cells of an epithelioid character make their way into the follicles, which are being depleted of their normal lymphocyte content. These cells are 3 or 4 times as large as the lymphocytes, and have a strongly eosinophile protoplasm ; they go through various grouping formations, resembling at times "cancroid pearls," and at certain stages are the most con-

spicuous cells in the follicles; they gradually lose their characteristic features, and, as the death of the animal approaches, their numbers become fewer and fewer. The significance of these epithelioid cells Heineke was not able to determine.

These observations refer to young guinea-pigs, mice and rats, the organs examined being the lymph glands, the spleen and bone-marrow.

This reaction to the rays is, however, not confined to young animals; Heineke found that adult rabbits and dogs exhibited a similar susceptibility, and that the modifications in the organs were very nearly as profound when the exposures were of the same duration as for the younger animals. If the exposure is not sufficiently long to cause the death of the animal, regenerative processes are soon set up in the lymphoid tissue, and an interval of 4–6 weeks is sufficient for a completely restored condition in this respect.

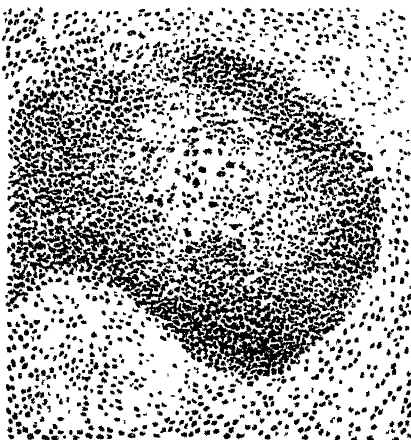


FIG 33.—Dog exposed to X rays for 2 hours, killed fifteen hours later.

Section through spleen follicle. Epithelioid cells are to be seen in the centre of the follicle, innumerable small spherical masses of chromatin between the lymphocytes.

Mitteilung aus den Grenzgebieten der Medizin u. Chirurgie (14). 1905.

Extending his observations to the thymus of young cats, Heineke found similar changes to those referred to above, but these changes require a longer period for their completion in the thymus than in the organs previously studied.

Reviewing the experimental facts gleaned from observations upon the spleen after exposure to X rays, Menetrier and Touraine point out that it is particularly the active centres of proliferation, viz. the lymphatic glands, which are affected by the rays; this action, they remark, is independent of any vascular or congestive process; it is, in fact, a direct action upon a particular variety of cells; the contrast in the effect of the same dose of X rays upon the lymphatic glands on the one hand, and the spleen and bone-marrow on the other, is in their opinion of special

significance when the treatment of leukæmia, lymphatic or myeloid, is in question. Their experience leads them to believe, as the experimental finding would indicate, that the former variety is much more amenable to X-ray treatment than is the latter.

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CHAPTER X

THYMUS AND THYROID

X RAYS. THYMUS.

NUMEROUS experiments have been conducted with a view to ascertaining the effects of the X rays upon the thymus. As early as 1903 Heineke observed that, together with the other lymphoid tissues, it underwent atrophy as the result of irradiation; interest in such experimental results was stimulated by the fact that abnormal persistence of the thymus is associated with a certain well-marked condition of cachexia in young children.

The normal thymus attains its maximum development in the human subject at about the end of the second year, from which period onwards it gradually shrivels away to a mere vestige. A section of one of the lobes of the thymus shows it to be made up of lobules marked off by trabeculæ of connective tissue. Each lobule consists of a peripheral part, or cortex, which is densely packed with lymphocytes, and of a central part or medulla, where the lymphocytes are much less closely packed. The lymphocytes of both cortex and medulla are supported by the meshes of a reticulum or stroma; the character of the reticulum renders the thymus unique among the lymphoid organs. In all other forms of lymphoid tissue the meshwork supporting the lymphatic cellular elements is composed of connective (*i.e.* mesoblastic) tissue cells and fibres; in the thymus this is not the case; the reticulum of the lobules consists of cells more or less stellate in form, whose branches anastomose freely to form the supporting meshwork, and which are derived from the epithelium lining the third embryonic branchial cleft; thus accounting for

the observation of Regaud and Cremieu that under certain conditions of irradiation these reticular cells revert to an epithelioid type. One other element of the thymus must be noticed, the Hassall's corpuscles. These are rounded structures of concentrically arranged cells, and situated at the centre of the lobules. By most authorities they are regarded as being specialised forms of the reticular cells; though Pigache and Beclère regard them as of lymphocytic origin.

In the present account of the effect of the X rays upon the

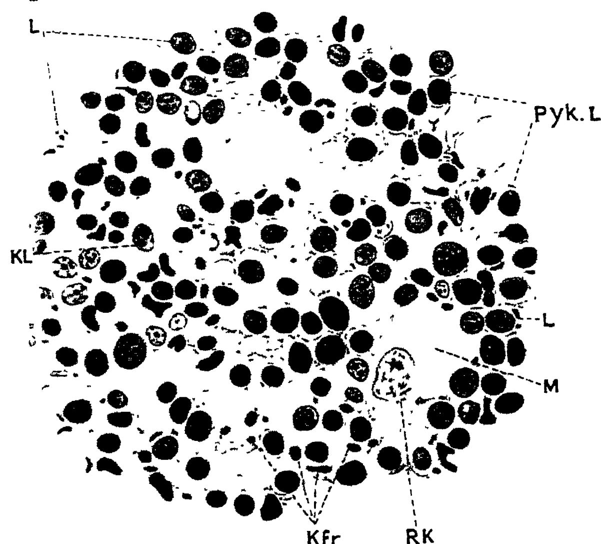


FIG. 34.—Rabbit, portion of surface of thymus, irradiated 5 hours. Killed half an hour after exposure was finished.

Section shows the different stages of lymphocyte destruction. *L*, unaffected lymphocytes. *Pyk L*, lymphocytes with pycnotic nuclei. *KL*, lymphocytes containing dark masses of chromatin. *Kfr*, fragments of nuclei. *RK*, reticulum nuclei. *M*, empty reticulum (masche).

Archiv für Anatomie. 1907.

thymus, the work of different observers must be considered separately; not only because different kinds of animal were used, but on account of variations in the technique of irradiation. As regards the broad outlines of the retrogressive changes which the organ undergoes as a result of exposure, there is very fair agreement; but the final results differ according to the duration and method of irradiation.

The first extensive and systematic series of observations upon the effect of X rays on the thymus are those of Rudberg (1907).

He used hard and medium hard tubes; the coil was run with a current of 3 amperes at 75 volts in the primary, the spark gap being 30 cm. As the subjects of experiments young rabbits, from one to four months old, were used, and irradiated for periods of from 1½ to 5 hours. Animals were killed at various times after irradiation, suitable control material being examined at the same time. In the first series the rabbits were irradiated for 5 hours, specimens being killed at intervals of from 12½ hours to 70½ hours after the commencement of irradiation. The thymus was, in the later specimens, noticed to be smaller; microscopically there was a disappearance of lymphocytes and degeneration in some of the cells forming the reticulum of the organ. With an irradiation lasting 3 hours, examination made half an hour after the conclusion of the exposure showed that the destructive processes had already begun in the lymphocytes. A specimen examined 13 hours after the conclusion of the exposure showed a complete destruction of lymphocytes; the killed lymphocytes undergo absorption by certain cells of the reticulum, and the process is complete in from 40 to 50 hours from the commencement of irradiation. The diminution in the size of the thymus as a sequel to irradiation is very striking, thus in two animals exposed for 5 hours, one killed after 2 days had the thymus reduced to less than a third of its normal weight; while in the case of the second, killed 3 days later, it was reduced to one-tenth.

The involution processes of the lymphocytes commence with pycnotic changes in their nuclei; this alteration is well advanced 3½ hours from the commencement of the exposure, and the nuclei are eventually represented by structureless lumps of chromatin, with strong basophile affinities. This destruction commences in a patchy manner in both the medulla and the cortex; at first, normal lymphocytes can be seen between the masses of débris, but they rapidly diminish in number, and at the end of 16 hours the cortex is seen to be full of their nuclear fragments, while they disappear from the medulla even sooner (in one example after 5½ hours).

At first the nuclear fragments lie free between the reticular cells; but soon (3½ hours) some of these latter are seen to have acquired phagocytic characters and to have ingested them. Initially these phagocytic reticulum cells do not differ in appearance from the normal, but with increased ingestion of chromatin

they become larger, lose their connection with the other reticular cells and assume a spherical shape. Such phagocytes are seen in the greatest numbers in the zone between the cortex and the medulla. The ingested nuclear fragments lose their basophile character and become eosinophile. The cells composing Hassall's corpuscles take no part in these phagocytic phenomena.

The phagocytes themselves also undergo degenerative changes, they may be seen with deformed and otherwise atypical nuclei, while still containing the remains of the ingested lymphocytes. The destruction of these large cells and of the lymphocytes gives rise to spaces of fair size in which lies the nuclear débris. By the coalescence of several such spaces, cysts are formed which often also contain red cells from extravasated blood.

The digestive processes associated with phagocytosis are concluded first in the medulla where the nuclear fragments may entirely disappear, while in the cortex they are abundant. In the cortex their disappearance occurs first in the region adjacent to the medulla and progresses outwards, and after these processes the cortex itself may be reduced to a more or less atrophic condition. The net result of the various processes just described is to produce a total disappearance of lymphocytes and of the remains of their nuclei. This may be regarded as the end of the first stage of the involution process, and at this period the thymus has been reduced to about one-fourth of its normal weight. This lymphocyte reduction and absorption is completed at the latest two days after irradiation.

We have now to consider the second phase of involution in which destruction of the reticulum cells is the predominant feature. In the early stages of lymphocyte destruction, however, this process has already commenced. Large spherical cells make their appearance, and are characterised by having a clear brightly-staining cytoplasm with an extraordinarily regular, finely-reticulated structure. These cells can be traced through various phases of degradation to the ordinary cell elements of the reticulum; they frequently exhibit vacuolation and all degrees of nuclear degeneration. It may be noted that the retrogressive changes are not mucoid in character.

Up to the time of absorption of all the nuclear remnants of the lymphocytes, these spherical cells were relatively few; but they now rapidly increase in number, so that when the thymus has

reached its maximum degree of involution practically the whole parenchyma consists of these altered cells. So far as can be determined, this particular form of degeneration commences in the peripheral part of the medulla, close to the remnants of the atrophied cortex, from which situation the change can be traced progressively inwards. The cells of the inner parts of the medulla appear to possess a higher degree of resistance than those of the outer layers.

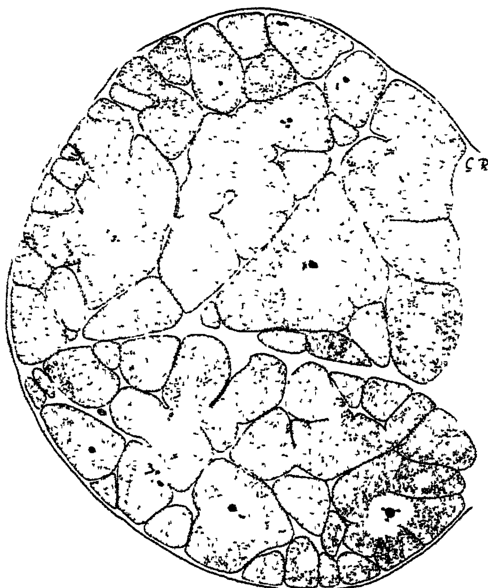


FIG. 35.—Cat. Transverse section of thymus of cat 28 days old. Magnification 22½ diam. The shaded region is the cortical zone, the clear region the medullary zone; the black portions represent the Hassall's corpuscles.

Archives d'Elec. Médicale. 1912.

Following upon these destructive changes, certain reparative processes may occur. In cases where the degree of irradiation has not been excessive, this takes place by proliferation of such lymphocytes and reticulum cells as may be left. Where the irradiation has been more severe in character, the more resistant central cells of the medulla undergo proliferation, and so regenerate the cells both of the medulla and of the less resistant cortex. Lymphocyte regeneration in these cases seems to occur by the proliferation of cells which come by the lymph channels, and,

passing along the perivascular connective tissue, penetrate to the centre of the lobules, whence they spread peripherally.

Pigache and Beclère studied the effects of irradiation, especially upon the Hassall's corpuscles, and came to the conclusion that these bodies were in reality degenerated lymphocytes.

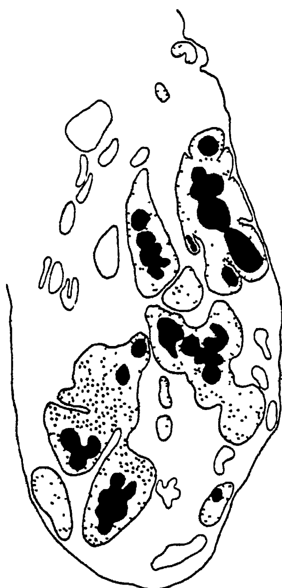


Fig. 36.

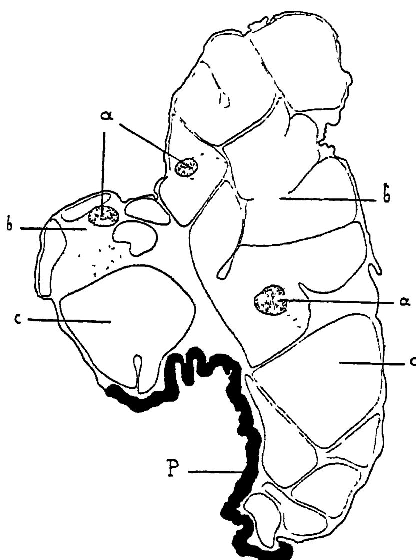


Fig. 37.

Fig. 36.—Cat. Transverse section of irradiated thymus of cat 40 days old, thirteen days after a single exposure to X rays. Magnification 22½ diam.

Marked diminution in size of medullary zones, hypertrophy of Hassall's corpuscles, enlargement of interlobular spaces and development of fatty lobules.

Fig. 37.—Cat. Transverse section of irradiated thymus of cat 4 months 6 days old, exposed on two occasions to X rays. Killed 2½ months after first exposure. Magnification 22½ diam.

Disappearance of normal thymus, parenchyma almost complete, there remain but three portions of cortical substance (*a*), and four portions of the stroma (*b*). There is a large increase in fat (*c*). (*p*) is a section of the pericardium.

Archives d'Elec. Médicale. 1912.

Regaud and Crémieu record the results of experiments upon a series of forty young cats. Special care was taken to irradiate only the region of the thymus, the rest of the body being protected by lead. The bulb was placed at a distance of 12–15 cms., and the rays filtered through aluminium screens .88 or 2.0 mm. thick. The dose was 14H, and, in the first series of experiments, a single exposure only was given. The first effect was diminution

in the size of the thymus; the retrogressive changes reached their maximum at the end of the second week, after which regenerative processes occurred, the organ being restored to nearly its normal size at the end of a month. As early as the second day after exposure there was noticeable reduction in size; on the fifth, the organ had lost 80 per cent. of its normal weight, while at the end of the second week the maximum degree of involution was obtained, and the thymus was found to have lost 90 per cent. of its normal weight. Microscopically the findings agree in the main with those of Rudberg; but Regaud and Crémieu did not find that all the lymphocytes underwent destruction and absorption, although this was true for nearly all of them. Two days was sufficient for their almost entire disappearance. The cells of the reticulum acquired an epithelioid appearance, and in many cases became transformed into cells whose characters were identical with those composing Hassall's corpuscles. This change is in accordance with the findings of Aubertin and of Bordet, who noted an enormous increase in the size of these bodies as the result of irradiation. About the fifteenth day reparative processes were distinct, the few surviving intact lymphocytes undergoing rapid proliferation. Between the 25th and 30th days regeneration was complete, and the thymus had regained its normal appearance, except that it was a little smaller than before irradiation.

It is thus seen that a single moderate exposure to the X rays produces a phase of marked regression followed by a return to an almost normal condition. Two further methods of experimental procedure were next adopted:

(1) Increased single dose (25H).

(2) Repeated moderate doses at intervals of from 6 to 10 days.

By both these methods a permanent condition of thymus atrophy was obtained. Three animals were allowed to survive for 22, 43 and 63 days after the irradiations, and in all cases the thymus tissue had either quite disappeared or was reduced to a mere vestige embedded in a mass of fat and fibrous tissue. The retrogression and cell destruction were so marked that any regeneration seemed impossible; Regaud and Crémieu considered that complete destruction could be ensured by the administration of a further dose of filtered rays.

Further experiments upon dogs are described by the same

authors. Five puppies, from 15 to 21 days old, were irradiated in a similar manner to the cats. The aluminium filter was 3.1 mms. thick, and the dose given was 20–22H. One animal was kept as a control. The thymus was markedly reduced in all the experimental animals; thus, while its weight in the control animal was 7.65 grammes, the weights in the irradiated puppies varied between 0.23 and 0.6 gramme. The histological findings were the same as in the rabbit and cat, with the single exception that the Hassall's corpuscles did not show the marked enlargement, a fact which may be accounted for by the small size of these structures in the normal dog's thymus.

The most recent studies upon irradiation of the thymus by X rays are those of Eggers. He irradiated young rabbits over considerable periods (8 to 12 weeks), exposures being for six minutes, a dose of from 1.5 to 2.0H being given every other day. His observations upon the histological changes accompanying regression broadly agree with those of Rudberg, except that he was unable to find evidence for the acquirement of phagocytic characters by certain cells of the reticulum. The structure which Rudberg regarded as phagocytes with contained cell débris, are considered by Eggers to be simply masses of degenerated cells whose protoplasm has undergone fusion. The most important part of Eggers' work, however, is the fact that after such prolonged irradiation regeneration occurs. In two animals irradiated over periods of 8 and 12 weeks respectively, and killed a month after the last irradiation, the gland was found upon examination to have regenerated almost to its normal condition; it may be added that studies were simultaneously made of the changes occurring in the blood cells, and Eggers regards further experimental work upon the subject as desirable.

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THYROID.

In a review of the experimental work on this subject up to 1911, Rave draws attention to the almost complete lack of recognisable effects resulting from the exposure of the thyroid to X rays.

Krause and Ziegler exposed the thyroids of mice, rats, rabbits, guinea-pigs and dogs under various experimental conditions, but failed to detect any changes, macroscopical or microscopical, which could be attributed to the radiation.

Experiments by Pfeiffer, and by Fiorentini and Louraschi, on similar lines failed to reveal any changes in the thyroids of dogs when exposed for quite long periods.

Rave's experiments were carried out upon rats and rabbits; although given comparatively large doses, ranging from 12X–36X, subsequent histological examination of the parts irradiated showed no changes as a result of the X-ray exposure.

The review mostly concerns itself with the clinical side of thyroid reaction to X-ray exposure, and draws attention to the marked effects which this form of treatment has upon the symptoms associated with pathological conditions of the thyroid, the effects upon the tissue of the organ itself being apparently of a very slight character.

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CHAPTER XI

DIGESTIVE TRACT AND GLANDS

STOMACH. RADIUM.

THE action of radium upon the stomach was investigated by Delbet, Herrenschmidt and Mocquot. Their method of experiment was as follows: five centigrammes of pure radium bromide were sealed in a cylindrical glass tube, which in turn was enclosed in a hermetically sealed silver tube 3 cms. in length, and with walls .5 millimetre in thickness. One end was furnished with a ring to allow of its fixture by suture to the stomach wall, while the other end was allowed to remain free.

The animals used in the experiments were dogs; a gastrostomy was performed to enable the tube to be placed *in situ* when it was stitched to the interior of the stomach wall, the free extremity being thus at liberty to execute a circular movement with the fixed end as centre. A second gastrostomy was performed 24 hours later, when the tube was removed. Four experimental animals thus treated were killed at intervals of 24 hours, 8 days, 15 days and 5 weeks, respectively, when the changes produced after those intervals by the 24 hours' exposure to radium were determined.

The general conclusions reached were as follows:

(1) The ultra-penetrating rays from 5 centigrammes of radium bromide, encased as described, and left in contact with the gastric mucosa for 24 hours, produce marked effects throughout the whole thickness of the mucosa. These effects are, however, preceded by a latent period of 8 to 15 days, during which time no obvious change is produced.

(2) The lesions produced by the irradiation in the mucous coat

do not extend to any degree beyond the field over which the free end of the radium tube can move.

(3) The superficial layers of the mucous coat do not appear to be more quickly or more severely influenced than the deeper ones. The first definite change which can with certainty be attributed to the action of the radium, and which is visible on the eighth day, is a hyperæmia accompanied by a certain amount of blood extravasation. No epithelial changes whatever can be made out.

(4) The connective tissue of the mucous and submucous coats undergoes stimulation and consequent hyperplasia. The more highly differentiated and sensitive epithelia exhibit only a small amount of resistance. The cells of the lining epithelium and glands of the mucous coat undergo destruction when in the immediate neighbourhood of the radium ; but at a little greater distance, when the intensity of irradiation is insufficient to cause destruction, they seem to undergo stimulation.

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STOMACH AND INTESTINES. X RAYS.

In 1912 Regaud, Nogier and Lacassagne made the important observation that X rays have a markedly destructive action upon the gastro-intestinal mucosa. Irradiation of the abdominal region in dogs by filtered X rays produced lesions which in some cases were rapidly fatal, and in others of a severe and permanent character. Filtration of the rays was effected by aluminium screens from 2 to 4 mms. in thickness.

Stomach. The superficial epithelium lining the stomach wall between the orifices of the glands is very insensitive to irradiation, and the same is true of the glands themselves in the pyloric region. The glands of the fundus are, however, highly sensitive, and, if the animals survived long enough, were found to have undergone almost complete atrophy. Of the two varieties of cell found in the glands of the fundus the parietal cells are the less sensitive.

Intestine. In the small intestine the chief effects are produced upon the villi, the glands of Lieberkühn and the lymphoid elements. In the villi, detachment of the covering epithelium first occurs, and this is followed by shrivelling of the stroma, destruction of cells and the final disappearance of the villus itself, in situations where the irradiation has been sufficiently intense.

In the case of Lieberkühn's glands, a sufficiently severe exposure leads to almost complete cell destruction, and consequent disappearance of the glands in a few days. Medium and even feeble doses may produce diminution in size, due partly to destruction of some cells and reduction in the size of others.

The lymphoid tissue of the intestinal wall was injuriously affected, but not to the extent that the observers had anticipated in view of the remarkable sensitiveness of this structure to the X rays. Other experiments by the same authors led them to the opinion that the intestine of the rabbit is less sensitive than that of the dog.

The rapid and destructive action of the rays will be best seen from the consideration of one or two of the original experiments. The following is of interest as showing the rapidity with which death may occur as the result of a single exposure. A bitch weighing 13 kilos was irradiated for one hour through a 2 mm. aluminium screen, care being taken to protect the spleen and liver as far as possible. The dose was 10H, the anode being placed 25 cms. from the skin. At the end of the exposure the animal was noticed to be suffering from diarrhœa, associated with marked gurgling noises in the intestine. Thirty-six hours later death occurred, the whole digestive tract was intensely congested and covered with abundant blood-stained mucus; there was no evidence of peritonitis. Another animal, 15½ kilos in weight, was irradiated for 85 minutes through a 2 mm. aluminium screen; the bulb was "soft" and the dose given 5H. Nine days after irradiation it was found to have lost 1 kilo in weight, and 12 days after this was given a meal of fowl bones, of which it partook in company with two control animals. These latter remained well, but the irradiated one died two days later. Commencing peritonitis was found, but there was no evidence of perforation. It would seem in this case that the irradiation had lowered the resistance of the intestinal wall, and the slight trauma

resulting from the meal of bones was sufficient to allow of infection of the peritoneum from the intestinal cavity.

A third experiment in which the animal (originally weighing 6 kilos) was kept alive nearly fifteen months, is of interest as showing the atrophic changes produced in the glands of the fundus of the stomach. In this case care was taken, as far as possible, to irradiate the stomach only to the exclusion of the intestine, and the exposures were repeated. The accompanying data indicate the progress of the experiment.

Date.	Bitch Weight, 6 kilos. Quite healthy.
24th Jan., 1911	Irradiation of stomach through abdominal wall. Aluminium filter, 2 mms. thick. Dose, 9H. Duration of irradiation, 70 minutes. Injection of 3 centigrammes of morphine to produce anorexia.
27th ,, ,,	Animal showed no inclination for food for three days after irradiation.
11th Feb. ,,	Second irradiation as before. Dose, 9H.
2nd Mar. ,,	Third irradiation as before. Dose, 9–10H. Weight, $5\frac{1}{2}$ kilos.
13th Nov. ,,	Fourth irradiation. Whole abdomen irradiated. No morphine. Dose, 14H. Aluminium filter, 3 mms. Animal remained two days without eating. Weight, $4\frac{1}{2}$ kilos.
6th Mar., 1912	Fifth irradiation. Whole abdomen irradiated. Filter, 4 mms. aluminium. No morphine. Dose, 22H. Weight, 4.3 kilos. The animal was very ill after this irradiation; remained curled up in the kennel, ate nothing, and had diarrhœa, with passage of blood.
3rd April, ,,	Died. For three weeks previous to death the animal became weaker and hardly ate anything. Emaciation extreme.

Post-mortem the gastro-intestinal tract was empty of food, but the intestine contained a remarkable number of tæniæ; there was no peritonitis. Microscopical examination of the stomach showed atrophy of the glands of the fundus, the principal cells of these glands being more damaged than the parietal.

The effects of irradiation upon the intestine are seen in the following experiment :

Date	Bitch. Weight, 17 kilos Good health
9th July	Irradiation of whole abdomen. Duration, 65 minutes. Screen, 0.92 mm. aluminium.
10th ,,	Second irradiation. 15 hours after the first. Duration, 88 minutes. Screen, 0.92 mm. aluminium. The total dose given in the two exposures was 70–75H.
11th ,,	Animal remained 36 hours after first irradiation without showing any symptoms, but then ceased eating, and remained crouched in the bottom of its kennel.
12th ,,	Killed.

The histological findings were as follows :

Stomach. Degenerative changes were noted in the principal cells lining the glands of the fundus, these being shrivelled and partly desquamated. Marked diapedesis of leucocytes had occurred towards the free epithelial surface. The pyloric glands were unaltered, the only change noticeable in the pyloric region being diapedesis.

Small Intestine. The lining epithelium was damaged and detached from the surface of the villi, the stroma of which was also reduced in amount and damaged. The glands of Lieberkühn showed marked changes, the cells being shrunken and degenerated, and in even such a short time after exposure to X rays these structures had in places almost disappeared.

Large Intestine. The glands of Lieberkühn showed changes similar in character though less in degree to those of the small intestine.

In one animal subjected to irradiation, acute peritonitis occurred as a sequel to perforation, which had apparently been caused by the presence of some hard substance in the food. Marked degenerative changes were present in the intestinal mucosa, especially in the region of the perforation.

The practical therapeutic bearings of this work are sufficiently obvious, especially in cases where abdominal organs are subjected to filtered rays.

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LIVER.

In his researches on the liver, Thies laid bare that organ in a guinea-pig, and applied the radium capsule containing 20 mgms. of radium bromide to its surface for six hours; at the end of this time the radium was removed, and the wound closed and dressed. Examination, twenty-four hours after exposure, showed local hyperæmia, both beneath the capsule and in the liver tissue itself. In the latter case the engorgement was most marked in the immediate neighbourhood of the central veins of the lobules, and diminished towards their periphery. Hæmorrhages were noticed occasionally in the regions of most marked hyperæmia, and there was an increase of eosinophile cells. The liver cells themselves showed some degree of swelling, while the bile ducts and the capsule presented no alteration.

At the expiration of four days, the liver cells exhibited marked alterations. The typical orderly arrangement was lost, the individual cells were isolated from one another and had become oval or round in outline, while in some places they showed atrophy, and had lost their nuclei. Commencing necrosis occurred in patches, the groups of necrosing cells forming islets surrounded by granulation tissue mixed with liver cells and lymphocytes. These liver cells frequently showed swelling, but the nuclei stained well; the cytoplasm sometimes appeared reduced to a ring at the periphery of the cell. The connective tissue of Glisson's capsule was infiltrated with leucocytes.

Examined nine days after irradiation, the exposed part showed only relics of liver cells, in the shape of homogeneous, non-nucleated, granular masses, but a kind of shadow of the original arrangement of the cells could be distinguished. Between the necrotic masses, capillary hæmorrhages were discernible, and in addition, new bile ducts lined with cylindrical epithelium were formed in the connective tissue; the liver capsule was thickened. On the fourteenth day, the process of repair had progressed, the necrotic areas were smaller and less numerous, while the normal liver tissue was separated from them by large quantities of

granulation tissue. The necrotic changes in the liver cells, and the separation and compression of the necrotic areas by newly-formed connective tissue, are also mentioned by Horowitz.

Mills investigated the action of the gamma rays upon the livers of mice. A small quantity of radium was used (applicator of 500,000 units; this corresponds to about .25 mgm. radium bromide), and applied over the region of the liver for about 30 minutes.

The main effects observed by him were:

(1) A transient change in the liver cells somewhat resembling a "cloudy swelling."

(2) An early inflammatory reaction lasting a few days.

(3) A late inflammatory reaction appearing in about 14 days and lasting much longer than (2).

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SALIVARY GLANDS.

Horowitz inserted his 1 mgr. tube of radium bromide into the submaxillary salivary gland of a rabbit; it was left *in situ* for ten days. The organ did not show itself very sensitive to irradiation, though local destruction of glandular tissue occurred, repair being effected by the formation of fibrous tissue.

PANCREAS.

Under the same conditions, the pancreas behaved precisely like the submaxillary salivary gland.

KIDNEY.

Horowitz inserted a tube containing 20 mgrs. of radium bromide into the kidney of a rabbit, and left it *in situ* for ten days; this produced localised necrotic changes. Short periods of irradiation merely produced a pronounced hyperæmia.

Buschke and Schmidt investigated the changes set up in the kidneys of rabbits and guinea-pigs when they are exposed to X rays for considerable periods. The kidney was exposed direct to a "medium" X-ray tube for periods ranging from ½–2 hours; after the lapse of a week, necrotic changes were observed, starting from the surface of the kidney and extending to some depth in the organ. These changes were only observed when the exposure was as much as 2 hours. The authors remark upon the relative insusceptibility of the organ compared with the testicle, when exposed to the same amount of X rays.

Heyman exposed rabbits to X rays for periods of 15–90 minutes; subsequent analysis of the urine showed an increased output of urea, of chloride and of albumin, but these conditions were only temporary. He observed a similar action upon the kidneys of the adult human subject, and found that the cells of the renal epithelium were but slightly affected under these conditions.

Warthin subjected rabbits, guinea-pigs, rats and mice to X rays for periods varying from ½–5 hours. The changes brought about in the kidneys consisted for the most part of nuclear changes of the renal epithelium, a diminution in volume of the cells, and a distension of the tubules caused by an albuminous precipitate. Warthin considered the action upon the kidney to be an indirect one, depending upon the destruction of leucocytes and the increase in secretion of urea. In two cases of leukæmia in the human subject, which had received prolonged X ray treatment, Warthin observed in the kidneys certain changes of a degenerate character.

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CHAPTER XII.

THE NERVOUS SYSTEM

RADIUM.

We owe the first systematic investigations regarding the action of radium on the nervous system to Danysz. In 1903 this observer introduced a small tube containing 1 mgr. of active radium salt under the skin of the heads of young mice. As early as three hours after its introduction, signs of paralysis and ataxia were noted; four or five hours subsequent to this, marked tetanic symptoms appeared and in from twelve to eighteen hours from the beginning of the experiment the animals died. The same tube of radium was also introduced subcutaneously in the lumbar region of three guinea pigs (8–12 days old), and allowed to remain *in situ* twenty-four to twenty-nine hours. From one to three days after its insertion, there appeared paralysis of the hinder part of the body, with tetanic spasms of the legs. Death occurred in from six to eight days. Full-grown guinea-pigs and rabbits did not show these marked symptoms, although they died some weeks or months later. In this case, however, the cause of death was complicated by the fact that sufficient time had elapsed for severe ulceration of the skin to occur, and the ulcers moreover, became septic.

A further experiment was done upon a full-grown rabbit. The animal being trephined, the radium tube was allowed to remain eight hours in contact with the dura mater. For two days no change was noticeable, but on the third a left hemiplegia set in. Subsequently hæmorrhages were found in the central nervous system, but no alterations were detected in the actual nerve elements. Danysz concluded that the central nervous system is very sensitive to radium radiations, and that older animals are more protected than young ones, owing to the thickness of their bones.

Analogous results were also obtained by Heineke (1903). In 1905 Obersteiner investigated the question afresh, paying special attention to the histology of the central nervous system. He employed white mice, confining them in small cages for periods of from twenty-four to ninety-six hours; in the lids of the cages a small aperture permitted the rays from the radium capsule to act directly upon the head of the animal. Two capsules were employed, one containing 50 mgr. and the other 10 mgr. of radium bromide. Of the thirty-six mice originally exposed, thirty-one died; the time of death varying between twelve hours and sixty-six days after irradiation. On examination, even macroscopically, hyperæmia of varying degrees was noticed in the meninges and in the substance of the central nervous system. The meningeal vessels had undergone such distension that they pressed upon the cortex cerebri to such an extent that they were completely embedded in it. In many cases hæmorrhages, often of considerable extent, could be detected, and fatty degeneration was noticed in the vascular endothelium. Obersteiner came to the conclusion that irradiation by radium, as such, had no specific effect upon the nerve substance, and that such derangements as occurred were fully accounted for by the circulatory disturbances consequent upon the injury to the small vessels.

Horowitz (1911), using a thin-walled glass tube of radium bromide, which was embedded in the substance of the brain or spinal cord, records a diminution of the chromatin of the nerve cells, and a thickening of the nerve fibres.

The action upon the peripheral nerves was studied by Okada. He irradiated the sciatic nerves of young rabbits. Three of the animals had two exposures, each of twenty-four hours' duration, the intervals between the exposures varying from two to seventeen days. A fourth animal had only one exposure of twenty-four hours. Strong cutaneous reactions, including ulceration, were produced in all cases, but the nerves showed no alteration. Similar experiments upon the sciatic nerves of rabbits and frogs were made by Scholtz, but also with a negative result. Horowitz, using the same tube of radium before mentioned (1 mgr. radium bromide), inserted into the nerve tissue, obtained atrophic changes in the axis cylinders and destruction of the myelin sheath.

Horsley and Finzi have shown that the brain substance of monkeys is distinctly insensitive to the gamma rays from con-

siderable quantities of radium. A tube of platinum .5 mm. thick, covered with rubber 1 mm. thick, and containing 55 mgms. radium bromide, was placed on the brain substance itself, a small piece of the skull having been removed for this purpose. The tube was left in position for 2½ hours in each of two experiments, the animal during this time being anæsthetised. The animals exhibited no untoward symptoms up to the 26th and 31st days, when they were killed.

As regards the nerve tissues, no discoverable change was present in either nerve cells or neuraglia, except in regions where hæmorrhages or thromboses had occurred, *i.e.* in the first two or three layers of the cortex. From the fact that under this same radiation notable changes were found in the blood-vessels, it may be inferred that the nerve cells are certainly not to be considered as sensitive to the rays. The change in the blood-vessels consists for the most part of collections of erythrocytes, which have passed into the perivascular lymphatics, distending them, the extravasation frequently extending into the surrounding neuroglia.

(For the effect of radium upon the developing central nervous system, *vide* section on its action upon development, p. 128.)

The action of radium emanation upon the brains of various animals was made the subject of a communication by Bagg, Ewing and Quick in 1920. Four methods of application were employed.

(1) Unscreened emanation in small quantities (.2 to 1.5 millicuries) inserted beneath the scalp, in rats. In other small animals it was inserted directly into the brain tissue.

(2) Larger quantities of emanation (65 to 255 millicuries) inserted into the brains of rabbits and dogs.

(3) Emanation screened by 1 millimetre of lead placed in the brain of a dog for thirty-five minutes.

(4) Doses of radium emanation corresponding to 4000 or 9000 " millicurie-hours " applied externally to the heads of two dogs, and an application corresponding to 12,030 millecurie-hours applied over the left temporal region of a monkey. In these cases heavy filtration was used.

The main results of these investigations showed that when small doses of unfiltered emanation were embedded in the brain a very localized area of necrosis occurred, and this was surrounded by a well marked polymorphonuclear infiltration.

When large doses of unfiltered emanation were embedded for a short time, a much greater destructive effect was produced than with small doses acting for a long time, notwithstanding the fact that the total number of millicurie hours was the same in both sets of experiments.

The external application of large doses of heavily screened emanation gave rise to comparatively slight damage only.

The large destructive effect of a large dose acting for a short time as compared with that of a small dose acting for a long time is similar to the result obtained by Mottram and Russ by the application of β rays to the human skin. In this case also a more profound disturbance resulted from a source of high intensity acting for a short time than from a source of low intensity acting for a long time.

Another finding of considerable interest in these studies upon the brain is that when unfiltered rays were used a considerable destruction of brain tissue resulted when a small dose was allowed to act for a prolonged period, but these were comparatively slight symptoms of neurological disturbance. If, on the other hand, a heavy dose was allowed to act for a short period, pronounced neurological changes resulted, generally with a fatal issue in a few days.

From a histological study of the brains of the animals into which metal tubes containing radium emanation had been inserted Bagg concluded that the resulting degenerative changes in the nervous tissues were secondary to a destructive action of the radiations upon the blood vessels, thus corroborating the findings of Obersteiner to which reference has already been made. As regards the nervous tissue itself Bagg concluded that it is highly resistant to γ radiations. In the case of a monkey which received a heavily filtered dose of emanation over the brain, there was no subsequent loss of previously acquired motor habits. As a practical deduction from his observations Bagg considers that the application of heavily screened emanation over the scalp is a relatively safe procedure for the treatment of brain tumours.

In 1922 Morowoka and Mott published the results of their examination of the brains of animals which had been exposed to the γ radiations from 5 grammes of radium bromide (RaB_2, $2H_2O$). The studies were made upon a series of thirty animals, including rats, rabbits and cats. No special attention was paid to the

occurrence or otherwise of any nervous symptoms occurring during life, the authors confining themselves to a report upon the histological appearances of the brain.

In a rat exposed for forty-eight hours, and in which death occurred two days later, the following changes were reported. In the cortex cerebri only a few cells retained their characteristic pyramidal shape, their processes were but indistinctly seen, and the nuclei were swollen and eccentric. On closer examination, with the oil-immersion, it was seen these nuclear changes were very marked Greatly swollen, the nuclei were found to occupy nearly the whole body of the cell, while the nuclear membrane showed infolding, and a certain degree of vacuolation of the nuclei was present. The cytoplasm was almost devoid of basophile substance, which where present existed merely as a fine dust-like deposit.

The cells at the base of the brain presented less marked changes. In the choroid plexus the cells showed great diminution of cytoplasm, swelling and unusually dark staining of the nucleus, and the differentiation between nucleus and cytoplasm was markedly indistinct.

In the cerebellum the layer of granules appeared well stained, as did also the Purkinje cells when examined with a low power. Upon examination with an oil-immersion objective the Purkinje cells exhibited a curious change. The chromophilous substance in many cells appeared displaced to one side in the shape of a crescent, while in other cells diffuse staining occurred.

In the large cells of the Pons Varolii marked changes were seen, the nuclei being in many cases much swollen and showing but poor differentiation from the cytoplasm. Nissl granules were absent, and on examination with a high power no definite nuclear membrane could be seen. The nucleolus was deeply stained and around it was an irregularly stained area, which in turn was surrounded by an irregular space traversed by fine threads and merging into the cytoplasm. In some case the nucleus appeared to have undergone complete destruction, and in none was the nuclear membrane distinctly seen.

In the cats the changes observed were slight and inconsiderable as compared with those occurring in the rats. In the rabbits the cerebellar Purkinje cells showed marked chromatolysis, but the chromophilous substance was not displaced to one side as noticed in the case of the rats.

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X RAYS.

The first publication dealing with the action of X rays upon the nervous system was a communication by Rodet and Bertin-Paris to the Congrès de Médecine Interne, held at Montpellier in 1898. They recorded two cases in which, in addition to the formation of extensive cutaneous sores, the destruction of the finger nails and other superficial lesions, marked nervous symptoms were a prominent feature. These consisted of a form of paraplegia, which was soon complicated by the development of disorderly and generalised tonic and chronic muscular contractions. Death occurred in eight and twelve days respectively, after the onset of these prominent nervous phenomena. The autopsies revealed a condition of meningo-myelitis.

Heineke (1903) exposed mice, guinea-pigs and rabbits "in toto" to comparatively large doses of the X rays. The mice were irradiated for periods of from five to ten hours in all, the exposures being made on several successive days. They died after six to ten days, of rapid emaciation and diarrhœa, but no peculiarly nervous symptoms were noticed. Guinea-pigs irradiated in all for from fifteen to twenty hours, died in from seven to fourteen days. In a great many cases, death occurred before the appearance of any cutaneous lesion. Heineke regarded the phenomena as due to some action of the rays upon the central nervous system, though he was unable to find any evidence of anatomical changes.

Dawson Turner and George (1910) exposed six young rabbits to X rays, with a view to determining whether brain injury was likely to result as a sequel to the administration of repeated doses of X rays to the head. In the experiments one side of the head was exposed to the rays while the other was screened by an eighth of an inch of lead. The coil used was an Apps giving a ten-inch spark, the tube was "medium hard," and twenty-five minutes was approximately the time requisite for the administration of a Sabouraud dose. Exposures were given at intervals of a week. Two of the animals accidentally died, the remaining four are accounted for thus :

(1) Died 5 days after first exposure (weight fell from 16 to 15 oz.).

(2) Received 3 exposures—died 9 days after last exposure (weight fell from 15½ to 13⅔ oz.).

(3) Received 2 exposures—died (weight fell from 13½ to 11 oz.).

(4) Received 3 exposures, weight fell from 17 to 16⅓ oz. : after the third exposure the experiment was stopped and the weight increased to 20½ oz. This animal was on the fifty-fourth day after the commencement of the exposure killed, and the appearances of the two sides of the brain were compared. The protected side was found to be better developed than the exposed. The large pyramidal cells were less developed, somewhat less numerous, and showed some vacuolation on the exposed side. An ophthalmoscopic examination made before death showed no changes in the retina.

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CHAPTER XIII

EYE

RADIUM.

THE first observations regarding the effects of radium rays on the eye were those of Birch-Hirschfeld in 1904. This observer applied a capsule containing 20 milligrammes of radium bromide to the closed eyes of rabbits for periods varying from four to six hours. The results of these exposures were identical with those obtained by the same observer when using X rays (see p. 253).

Action of radium rays upon the developing eye. This has been made the subject of investigation by Milroy, who employed chick embryos for his experiments. The eggs were exposed to the rays from 20 mgr. of radium bromide contained in a capsule with a thin mica floor, and the whole enclosed in a thick lead box, placed in an ordinary incubator. Development was allowed to proceed under these conditions for periods varying from seven to eighteen days, after which the embryos were directly exposed to the capsule for from one to three hours, a portion of the shell and membrane being carefully removed. After this the eyes were fixed and sectioned. In specimens incubated for seven days and treated as described, the eye presented but small deviations from the normal, though degeneration was noted in the retina and to a less extent in some of the other tissues; the lens was normal. As regards the retinal changes, the whole structure was thinner than normal and the degenerative changes were seen to affect all the cells of the retina; the pigment cells were swollen and their granules diffusely scattered through them, some being extruded into the tissues beyond. The nuclei of the retinal cells, instead of presenting their normal stratified arrange-

ment, showed irregular massing together. Mitosis was observed in the posterior retinal cells, but observations were difficult, owing to a falling together of the chromosomes. A considerable disintegration of the surrounding mesoblastic cells was also noted. In specimens examined at later stages of exposure and development, the changes were similar in character, marked destruction was seen in the ganglion cells and in the fibres of the optic nerve. In spite, however, of the markedly destructive power of the radium rays, it is, as the author says, "a remarkable thing, that development goes on, with the retina in the condition that it is." Thus, in specimens examined on the 15th to 20th days, the rods and cones can be identified, though these undergo destruction almost as soon as they are formed. The tissues which appear to be the least affected are the lens and muscle fibres; the retina is the most affected, and the radium rays do not in any case produce response in those cells which normally respond to light. The author regards the destructive effects upon the retina as mainly due to the gamma rays, and notes that the changes produced in his series of experiments closely resemble those obtained by exposure to X rays. The especial peculiarity of the degenerative effects of radium rays upon the retina lies in the fact that, though extensive cell destruction occurs, yet mitosis is not inhibited, and development proceeds to the formation of rods and cones, though these in their turn are again destroyed.

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X RAYS.

The effects of exposing the adult eye to the Röntgen rays were first studied by Birch-Hirschfeld in rabbits. A medium soft tube was used at a distance of 8–10 cms., the exposure being made for thirty minutes and the total dose given being 30H.

After a latent period, varying between thirteen and forty days, marked signs of inflammation made their appearance. Prominent among these were blepharitis, conjunctivitis and interstitial keratitis; the iris was hyperæmic and showed the presence

of a considerable amount of exudate. Some weeks later these inflammatory troubles gradually subsided, the most obstinate lesion being the keratitis. The retina and optic nerve, examined thirty-nine to sixty days after the exposure, showed disintegration of the retinal cells in the one case and optic atrophy in the other. By a further research (also upon rabbits) the same author showed that in adult animals an exposure of twelve minutes (dose 10–12H) does not produce retinal changes, while exposures of from fifteen to thirty minutes not only give rise to retinal degeneration, but also to optic atrophy.

Tribondeau at the *Réunion biologique,* held at Bordeaux in 1907, communicated the interesting observation that the crystalline lens, in the case of new-born animals, was exceedingly sensitive to the X rays, an exposure of five minutes being sufficient to produce cataract and consequent blindness. In conjunction with Lafargue, the same author performed a series of experiments upon the eyes of adult rabbits, with especial regard to any possible changes in the lens. In these cases exposures totalling thirty to sixty minutes were given. During life no changes could be detected in the lens by the ophthalmoscope and when the animals were killed six weeks later, a microscopical examination revealed nothing abnormal in its structure. The reaction of the lens to X rays therefore differs markedly in young and adult animals.

With a view to ascertaining whether any other changes occurred in the immature eye as a sequel to exposure to X rays, and whether these were in any way peculiar to the young, as distinct from the adult eye, Tribondeau and Belley irradiated the eyes of young kittens from one to five days old (*i.e.* before the eyes were opened). The irradiations were performed in such a manner that in each animal only one eye was exposed to the rays, the other eye thus serving as a control. These observers found that the lesions occurring as a result of irradiation fell into two groups. The first group comprised those lesions common to both the immature and to the adult eye, such as blepharitis, conjunctivitis, keratitis and modifications in the aqueous humour of the eye. In the second group were found those lesions which appeared to be characteristic of the immature as distinct from the adult eye; they were five in number:

(1) Premature opening of the eye.
(2) Delayed pigmentation of the iris.

(3) Cataract.
(4) Diminution in the size of the eyeball.
(5) Peculiar degenerative changes in the retina.
(6) Changes in the vitreous humour.

(1) *Premature opening of the eye.* The irradiated eye was invariably found to be open several hours before the control. This was due to the earlier destruction of the cells which unite the upper and lower lids in the young animal. Although, however, the irradiated eye was open before the non-irradiated, the palpebral cleft remained permanently smaller and narrower.

(2) *Delay in pigmentation of the iris.* The iris of the normal unopened eye of the kitten is of a peculiar slate colour, which, when the eye opens, gives place to the characteristic yellow or green colour of the eye of the adult cat. In the irradiated eyes, this slaty tint of the iris persisted long after the control eye had attained its normal pigmentation; this occurred, for example, in one animal which was examined forty-five days after exposure.

(3) *Cataract.* This was easily discernible thirty-five days after exposure, though microscopical changes could be detected in the lens as early as the sixteenth day. The equator of the lens was the first part to be affected, and, on examination with a hand-magnifier, showed a zone of small confluent vesicles. On microscopical examination, striæ and flocculi could be observed, most marked at the periphery, but gradually permeating the whole body of the lens until complete opacity was produced. The eye under such conditions was of course blind, but the light reflex was not abolished. Gradually the lens diminished in size, the anterior chamber of the eye becoming deeper in consequence. Microscopical examination of the irradiated lens at different periods showed that the first part to be affected was the epithelium covering its anterior surface, the component cells becoming flattened and in places disappearing, so that portions of the lens were completely denuded of epithelium. The lens fibres become enlarged, tortuous and irregular, in addition to showing vacuolation and granular changes.

(4) *Diminution in size of the eyeball.* The irradiated eyeball was invariably smaller than the control, and this was observable after quite short exposures; in one case examined fifty-two days after an exposure of only five minutes, the diminution in size was apparent.

(5) *Degenerative changes in the retina.* The retinal changes comprise a peculiar microscopic malformation of this membrane, which consists of proliferation and folding of the layers which make up its anterior half or two-thirds. These foldings and proliferations are most marked in the region of the *ora serrata.*

(6) *Changes in the vitreous humour.* An opacity in the vitreous humour, which in sections of the eye appears fibrillated, is associated with thickening of the hyaloid membrane.

As regards the effects of different types of rays, Tribondeau and Belley found that " soft " X rays produced the most damage to the superficial parts, while the lens was most affected by the " medium " and " hard " rays.

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CHAPTER XIV

MUSCLE, CARTILAGE, AND CONNECTIVE TISSUE

STRIATED MUSCLE.

WHEN Thies investigated this tissue in the guinea-pig, the capsule (20 mgr. radium bromide) was enclosed in an envelope of sterilised rubber tissue, and then placed directly upon the exposed muscle for six hours. At the expiration of that time, the skin incision was closed and the wound dressed with collodion. After the lapse of six hours, marked vascular changes were noticed in the inter-muscular tissue, viz.: engorgement of vessels, diapedesis, and infiltration by polymorphonuclear cells, lymphocytes and eosinophiles. After twenty-four hours, there was further tissue infiltration and engorgement, while characteristic changes had also occurred in the vascular endothelium. Up to this point the observed changes were confined to the vessels and connective tissue, but after three days a destruction of muscle fibres could be seen. Where the fibres persisted, striation was still detectable, and the nuclei of the sarcolemma were present. Here and there, in place of the normal muscle fibre bundles, was only a band of closely approximated flaky and homogeneous material, which stained well with eosin. A marked increase in the amount of connective tissue had taken place, and numerous fibroblasts, lymphocytes and polymorphonuclears were found together with occasional plasma cells. After five days the irradiated part was found to have lost most of its colour, the vascular changes were still very marked, and the muscle fibres replaced by connective tissue; between the connective tissue elements, however, the remains of muscle were still observable, though the nuclei of the sarcolemma had disappeared.

On the fourteenth day connective tissue formation had progressed so as to form the beginnings of a fibrous scar.

Horowitz has described similar degenerative changes in the muscular tissue of the rabbit.

The action of beta and gamma rays upon the striated muscle of the rabbit has been studied in detail by Lacassagne. He inserted very small glass tubes containing radium emanation into the lumbar muscle of the rabbit and found that a zone of necrotic tissue surrounding the tube was formed in course of time. The extent of this zone varied with the amount of emanation in the tube, and microscopical examination showed that a comparatively sharp line of demarcation separated this zone from the tissues beyond it. The extent of the necrosis was found also to depend upon the degree of filtration of the beta and gamma rays; the most pronounced effects being obtained with the least amount of screening. For an unscreened tube containing 16 milli-curies the radius of the zone of necrosis was 7 mms. With this same concentration when the tube was screened by 1 mm. of platinum the radius of the zone was reduced to 1.5 mms. Lacassagne refers in some detail to the bearing which these observations have in radium therapy. He considers that changes amounting to complete necrosis of the tissues are to be carefully avoided in therapy, because extensive necrosis may give rise to many undesirable sequelæ; such foci may help to spread bacterial infections, also if the damaged tissue happens to be a blood vessel, serious lesions may result. The paper contains data which appear to have many direct applications in radium-therapy.

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HYALINE CARTILAGE.

Among the tissues subjected to the action of radium by both Thies and Horowitz, hyaline cartilage presents special features of interest, since it undergoes a quite definite hypertrophy as a

result of exposure. Thies carried out his experiments by exposing the ensiform cartilage of guinea-pigs, and directly irradiating it with 20 mgrs. radium bromide for six hours. Twenty-four hours subsequently no changes were visible on macroscopic examination. Histologically, the nuclei of the superficial cartilage cells were found to be destroyed, as were also those of the cellular elements of the perichondrium. Between the perichondrial connective



FIG. 38.—Irradiation of the hyaline cartilage of the guinea-pig. The section was taken 14 days after irradiation.

tissue fibres were numerous free red-blood corpuscles, polymorpho-nuclear cells, lymphocytes, and, in smaller numbers, eosinophile cells, while the blood-vessels showed marked engorgement.

Five days after the application of radium the superficial layer of the cartilage appeared broadened, and contained large round cells ; the nuclei of the cells were rounded, contained a fair amount of chromatin, and were surrounded by a small clear perinuclear space. The cartilage cells in this superficial zone were somewhat irregularly arranged, while in the more central portions they were

enlarged and swollen. There was marked thickening and hyperæmia of the perichondrium.

On the fourteenth day (the original wound having now completely healed), a thickening could be detected in the region of the ensiform cartilage. On examination, the superficial parts of the cartilage were found to contain cells with four or five nuclei in place of the typical mononucleated cartilage cells. The perichondrium presented deviations from the normal type; its



FIG. 39.—Normal hyaline cartilage of the guinea-pig.

connective tissue cells were enormously increased, and were arranged in a palisade-like manner upon the surface of the cartilage. Outside the palisade-like structure was a large number of spindle-shaped cells, with small nuclei staining moderately deeply, and having a definite cell body; these were mostly arranged in short bundles which interlaced irregularly. In their neighbourhood were numerous capillaries and small arteries; while between the cells were free red-blood cells, some lymphocytes and leucocytes, and a few eosinophile cells.

The initial change produced by the exposure of hyaline cartilage to radium is thus seen to be of a destructive character; sub-

sequently, however, this gives place to a marked hypertrophy of the cartilage substance itself, the nature and extent of which may be seen from Fig. 38 and Fig. 39, the former being the irradiated specimen.

It is interesting to note that this stimulating effect was also observed by Horowitz, when cartilage of the rabbit was exposed to 1 mgm., the duration of exposure being ten days.

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CONNECTIVE TISSUE.

Thies observed that the connective tissue, as seen in the preparation of skin, muscle and cartilage, when adjacent to a radium capsule, undergoes destruction. The cells lose their nuclei, the sharp outline of the fibrous elements is lost, and there is marked cell-infiltration in the vicinity of the blood-vessels. In regions which have not been so closely brought into contact with the radium capsule, however, the connective tissue is found to be considerably increased. The elastic fibres exhibit a marked resistance to the destructive action of radium, a character wherein they stand in marked contradistinction to the white fibrous and the cellular elements. Indeed, after prolonged irradiation, the elastic fibres may be perfectly distinct, although the rest of the tissue has undergone disintegration.

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CHAPTER XV

THE GENERATIVE SYSTEM

TESTIS. RADIUM.

THE changes resulting from the action of radium upon the testis do not appear to have been made the subject of such exhaustive histological analysis as those supervening upon exposure to X rays. Thies exposed the testicles of full-grown guinea-pigs, and submitted them directly to a radium capsule (20 mgr. radium bromide) for twenty-four hours. Examination fourteen days later showed a total absence of spermatozoa. The cells of Sertoli were still normally situated upon the basement membrane, but their nuclei were considerably swollen ; the true seminiferous epithelium was destroyed ; the tubules showed masses of disintegrated cell tissue, and in the central part of the tubule, instead of spermatozoa, were large cells with darkly-staining nuclei, rich in chromatin. The nature of these cells, which were large and cuboid in outline, could not be determined, as they did not conform to any normal type of seminal epithelium. The necrosis of the seminal epithelium in rabbits consequent upon exposure to 1 mgm of radium bromide has also been noted by Horowitz.

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THE ACTION OF X RAYS UPON THE TESTIS.

The action of X rays upon the testis has been made the subject of several exhaustive researches, and for two reasons. In the

first place there is the important physiological phenomenon, that prolonged exposure to these rays produces sterility; and, secondly, the testis itself presents unrivalled opportunities for cytological study. The organ is highly cellular, the cells are of different types, and the cytological changes involved by the development of the spermatozoa, through the stage of spermatid, spermatocyte, and spermatogonium afford ample opportunity for the observation of any abnormalities in the process.

The physiological phenomenon of sterility was first experimentally studied by Albers-Schönberg in 1903, the animals employed being rabbits and guinea-pigs. Moderately soft tubes were used, the animal being at a distance of 17 cms. from the anti-cathode. The exposures were given daily for periods varying from 15–30 minutes, and the total duration of exposure varied from 195 to 377 minutes. The irradiated animals were paired with untreated females, and though no loss of sexual potency was observed, in no case was a litter produced.

Frieben (also working with rabbits and guinea-pigs) in the same year demonstrated atrophy of the testes as a sequel to long exposure, and showed that the sterility was due to destruction of the epithelium lining the seminiferous tubules.

The first observations upon sterility produced in the human subject by X rays were published by Philipp in 1904. He records the cases of two men who were irradiated in the perineal region for therapeutic purposes.

The first was a case of tuberculosis, and daily exposures of from 10–15 minutes were given for 30 days, the total duration of exposure being 365 minutes. The tube was a medium soft one, and placed at 10–15 cms. distance. At the end of this time the semen was examined, and found to contain normal motile spermatozoa. Subsequently a resection of the vas deferens on both sides was performed, and six months later no spermatozoa were found in fluid withdrawn from the epididymis.

The second case was one of pruritus ani; a soft tube was used, but its distance from the subject is not given. The exposures given were as follows:

Jan. 12–17 - - -	ten minutes daily.
Jan. 19–28 - - -	ten minutes daily.
Jan. 31 - - -	fifteen minutes.
Feb. 1 - - - -	fifteen minutes.

Total exposure = 190 minutes.

After these exposures the patient was lost sight of, but after some months returned with a slight recurrence of pruritus; seven months later an examination of seminal fluid showed complete azoospermia. Only one examination seems to have been made.

In 1905, Brown and Osgood recorded the cases of 18 X ray workers, who were the subjects of complete azoospermia, or of oligonecrospermia. All of those examined, who had done extensive X-ray work for more than three years, showed complete azoospermia.

Before entering upon an account of the various histological findings as the result of experimental exposure to X rays, it may be well to give a short note on normal spermatogenesis. The description submitted here is an abstract of that given by Wakelin Barratt and Arnold in their researches upon the effect of X rays upon the testis of the rat.

A section of a seminiferous tubule shows a basement membrane at the periphery. In contact with this basement membrane are cells of three kinds:

(1) Cells of Sertoli;
(2) Spermatogonia;
(3) Spermatocytes of the first order.

Next come more spermatocytes of the first order, and the innermost layer of the tubule is formed by smaller cells of three kinds:

(1) Spermatocytes of the second order;
(2) Spermatids;
(3) Spermatozoa.

There is, however, some degree of intermingling of these different types of cells.

The development of spermatozoa proceeds as follows. The spermatogonia divide into two: one of the daughter cells remains a spermatogonium, the other becomes a spermatocyte of the first order. The spermatocytes of the first order in their turn divide, the resulting daughter cells being the smaller spermatocytes of the second order. These spermatocytes of the second order undergo division, their daughter cells being the spermatids. The spermatids undergo a series of changes, and become spermatozoa. Below is a description of these various cells and of the types of change which they undergo.

(1) *Spermatogonia.* These are small cells, with a relatively large nucleus and small amount of cytoplasm. They are somewhat flattened, and the nucleus contains three or four dark masses of chromatin, connected by fine strands of linin. Division (of the somatic type) produces two daughter cells, both at first identical in appearance with the parent spermatogonium. Subsequently one of the cells becomes a spermatocyte of the first order, while the other remains a spermatogonium.

(2) *Spermatocytes of the first order.* These undergo a series of changes which terminate in the "first maturation division" ("heterotype" or "first meiotic division"). The changes may be summarised thus; the chromatin masses become distributed along linin threads which increase in number, and the chromatin appears as a fine network; this network becomes coarser and forms a spireme, the spireme threads shorten and form the heterotype chromosomes, which vary in shape—loops, rings and rods. Meanwhile the two centrosomes originally present in the archoplasm leave the latter, and migrate to opposite sides of the nucleus, a spindle being formed between them. The nuclear membrane now breaks down, and the chromosomes become attached to the spindle fibres. Migration of the chromosomes to the respective poles occurs, and the formation of the daughter cells or spermatocytes of the second order is completed.

(3) *Spermatocytes of the second order.* These cells have a nucleus with a well-marked nuclear membrane and a sparse network of chromatin. In the cytoplasm are the archoplasm, and the remains of the nucleolus of the first order—the "chromatoid body." This structure is also seen in the spermatid, and serves as a means of differentiating these cells from the spermatocyte of the first order. A spireme is not formed; the chromatin network breaks up into a series of short rods which form the chromosomes of the "second maturation division" ("homotype," or "second meiotic division"). This division results in the formation of the spermatids.

(4) *Spermatids and spermatozoa.* The spermatid, mentioned in the preceding paragraph, next undergoes a series of changes to become the spermatozoon. The nucleus rapidly enlarges, the chromatin granules become progressively finer until it presents a nearly homogeneous appearance. In the cytoplasm an archoplasm is formed, in which small vesicles appear. These coalesce

to form one large vesicle, in the centre of which is a darkly-stained mass—the "intermediate substance" of Moore and Walker. The vesicle becomes somewhat flattened and spreads out over about half the nucleus, and the "intermediate substance" spreads out and becomes closely attached to the nuclear membrane; the vesicle thus forms a cap for the nucleus.

At the side of the nucleus opposite to this cap are the two centrosomes and the chromatoid body. When the cap has covered half the nucleus, a collar-like structure ("manchette") appears at the opposite end. This is derived from the cytoplasm and soon disappears; while it persists, however, it encloses the centrosomes and the chromatoid body. One centrosome now lies on the nuclear membrane and acquires a disc-like form; from the other centrosome is developed the axial filament of the tail of the spermatozoon. During these changes the cytoplasm has undergone elongation in the direction of the tail of the spermatozoon, globules of fat occur in it, and it is cast off, with the exception of a very small portion around the basal portion of the axial filament.

(5) *The cells of Sertoli* (*or foot-cells*). These cells, which do not develop into spermatozoa, are large, and have a broad base attached to the basement membrane of the seminiferous tubule. The nucleus is large, the chromatin distributed as very fine granules of uniform size, and no linin strands are visible. In the course of their development the spermatids become attached to these foot-cells by their cephalic extremities, and each foot cell eventually supports a large number of spermatozoa. The foot cells are distinguished from spermatozonia by their greater size, clear nucleus, large nucleolus and finely-granular chromatin.

(6) *Degenerations in cells of normal testis.* Certain degenerative changes are noted in the cells of normal testes, and consist of either necrosis or the formation of fatty globules.

(*a*) *Necrosis.* This is rare, and apparently only affects spermatocytes of the first order. It is recognisable in stained sections, by the fact that the cytoplasm of the affected cell takes up basic instead of acid dyes.

(*b*) *Fatty change.* This occurs in two forms, according as the fat globules are small or large. The small globules are chiefly disposed towards the lumen of the seminiferous tubule, while

the large ones tend to be situated towards the basement membranes.

(i) The small globules occur in the cytoplasm of spermatids during the development of the spermatozoon.

(ii) The larger globules are infrequent, and occur only in a minority of the tubules.

It may be added that the degenerative changes are most frequently observed during the non-copulatory periods when the testes diminish in size and are withdrawn into the abdominal cavity.

In 1904 came the classical researches of Bergonié and Tribondeau upon the testicle of the white rat. The body of the animal under the experiment was protected by a sheet of lead, perforated in such a manner that only the testicle was exposed to the rays. The animals were placed at a distance of 15 cms. from the anticathode, and the intensity of the irradiation was 4 Holzknecht units. The exposures varied in duration from 2 to 10 minutes, and were repeated at intervals of from 1 to 8 days. Macroscopically there was an appearance of softening, and the organ was more translucent. In the majority of cases, one testicle was removed immediately prior to exposure, in order to provide a control. Histological examination revealed different degrees of destruction of the spermatogenous epithelium. Mitotic figures had disappeared. Large spermatocytes were rare, and where still persisting, exhibited fragmentation of their chromatin; at first the disintegrated chromatin was arranged as a beaded spireme, but subsequently the fragments became scattered, stained badly, and finally disappeared; in rare cases pycnosis was observed.

The spermatids, small spermatocytes and spermatogonia persisted longer and exhibited pycnosis. Condensation of the chromatin into a mass at the side of the nucleus was observed in the spermatocytes and spermatogonia, while in the spermatids it was at first annular. The pycnotic nuclei broke up and then disappeared. In the different cells, however, a survival of chromatoid fragments was of frequent occurrence. The spermatozoa were still more resistant, but they finally adhered together and then dissolved.

The cells of Sertoli persisted. Their nuclei remained intact and stained well, soon underwent amitotic division, and invaded

the lumen of the seminiferous tubule. In the tubule, which had undergone even more destructive changes, the nuclei of the cells of Sertoli were found to be altered, stained diffusely, and were eventually unrecognisable. From these observations it can be seen that the destructive action of the X rays upon the cells of the seminiferous tubules is not a simple desquamation, but a profound chemical and morphological alteration, followed by resorption *in situ*. The nutritive syncytium persists for a long time, hollowed into spaces which at first contain chromatic débris, but subsequently become empty, though retaining the outline of the cells which originally occupied them.

Wakelin Barratt and Arnold published the results of an exhaustive series of experiments upon the testicle of the white rat in 1911. The details of the experiments are as follows: full-grown male rats with well-developed testes were selected; the animal was laid upon its back, with the testes 15 cms. from the anti-cathode, and the body—with the exception of the testicular region—was shielded from the rays by a sheet of lead, the tube being of medium hardness. The current in the secondary ranged from .6 to .7 milliamperes. A fifteen-minutes' exposure to the rays gave ordinarily a reading of one unit on the scale of Sabouraud.

Ultimate changes produced by X rays. There is a complete disappearance of the seminal cells. What should be the lumina of the seminiferous tubules are occupied by shreddy débris arranged perpendicularly to the basement membrane. Numerous large (Sertolian) nuclei are seen near the basement membrane, which appears intact. This shreddy material stains with acid dyes, and under a high power is seen to have a finely granular structure. As regards the nuclei above mentioned, the nuclear membrane is seen to be well defined, and the chromatin is evenly distributed in the form of extremely fine granules. One nucleolus is present, darkly stained and relatively large.

In what may be termed the penultimate stage of destruction, the lumina of the tubules are largely occupied by necrotic material and fatty masses, some of which are of considerable size. The shreddy material which preponderates in the ultimate stage is also present here, though in smaller amount. Some of the most characteristic changes are illustrated in Figs. 40 and 41.

Changes produced in the different elements of the testis. If

a testis is removed and examined immediately after exposure, no changes whatever are observed. If, however, 24 hours are allowed to elapse between exposure and removal, definite changes

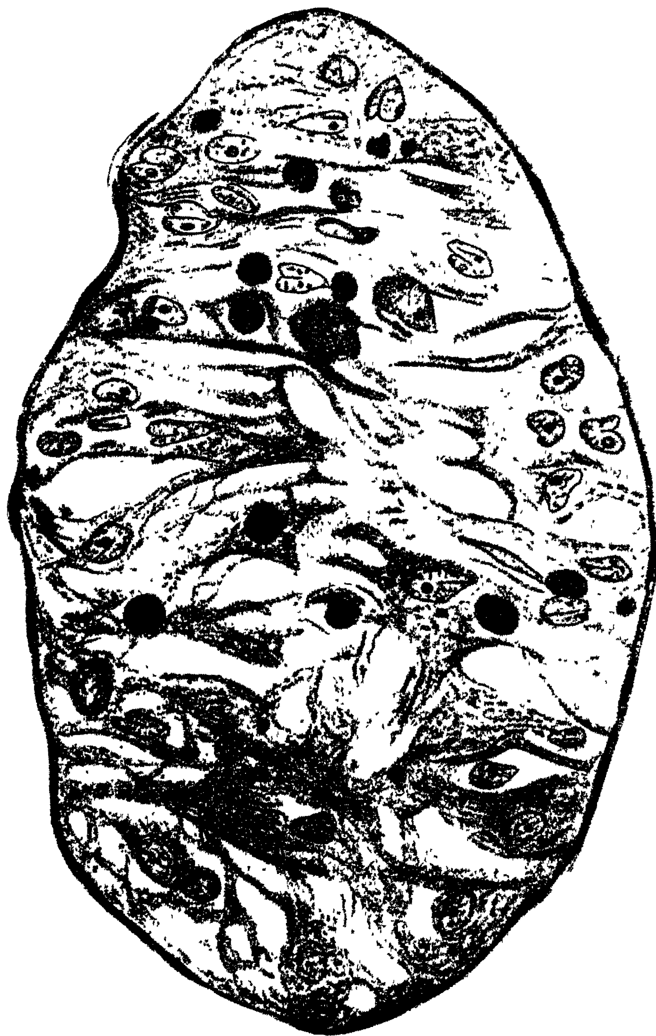


Fig. 40.—Seminiferous tubule thirteen days after the application of X rays. All the seminal cells have disappeared. Externally the basement membrane is seen. Distributed within the tubule are numerous nuclei of cells of Sertoli, the cytoplasm of which forms a coarse framework, within the meshes of which fatty masses, more or less darkly stained with osmic acid, are sparsely scattered. No definite lumen is present in the tubule

Wakelin Barratt and Arnold, *Archiv für Zellforschung*, vol. 7. p. 242. 1911.

can be made out with the higher powers of the microscope, though under a low power little, if any, alteration is discernible.

In investigating the results of moderate irradiation, it is necessary to remove one testis immediately before the exposure, so as to have a control. This is required in view of the fact that non-irradiated testes may themselves present slight degenerative changes.

(*a*) *Changes in the interstitial tissue.* At the end of a week after prolonged exposure, the gland has already decreased in size, but at the same time is œdematous, clear fluid exuding freely on incision. Microscopic examination, at this time or a week later, shows merely some distension of the connective tissue spaces. The nuclei of the interstitial tissue are unchanged in number or appearance; there is no cell infiltration, and the blood-vessels are unaltered.



FIG. 41.—Portion of a healthy seminiferous tubule for comparison with the preceding figure. To the left the basement membrane is seen. To the right of this lie the seminal cells, among which are recognisable spermatogonia (in contact with the basement membrane) cells of Sertoli, spermatocytes of the first order, spermatids and spermatozoa, the tails of the latter being free in the lumen of the tubule. Near the basement membrane large fatty masses are seen; towards the lumen of the tubule collections of small fatty globules lying within the cytoplasm of the spermatids are shown.

Wakelin Barratt and Arnold, *Archiv für Zellforschung*, vol. 7. p. 242. 1911.

(*b*) *Cells of Sertoli.* These cells exhibit the most marked changes about 14 days after prolonged exposure. The seminal cells have then been destroyed, and the cells of Sertoli are greatly increased in number. The cytoplasm is diminished in amount, its margins ill defined and ragged, while it exhibits a very coarsely reticular and occasionally vacuolated character, and stains but lightly. The nucleus is unaltered in size, but presents one or more clefts.

In the earlier periods the changes are less marked, but as soon as the fourth day after exposure, an increase in the number of cells of Sertoli can be made out, and the shreddy débris (which was present in large amounts in the 7 or 14 day specimens)

has begun to appear. This material is generally regarded as the remains of the cytoplasm of the cells of Sertoli.

(*c*) *Spermatogonia.* After a moderate exposure these cells persist for about three days, but after the fourth day they cease to be observable. No necrotic or other change can be detected in the cells while they persist, but there is a total absence of any mitotic figures. This absence of mitosis affords one explanation of the great diminution of the next group of cells—the spermatocytes of the first order—after a moderate irradiation.

(*d*) *Spermatocytes of the first order.* During the first few days following exposure, these cells develop marked changes, and owing to their large numbers and prominent characters, their alteration is responsible for a great deal of the changed appearance of the seminiferous tubule. The alterations in these cells are of two kinds, necrotic and non-necrotic.

(1) *Necrotic changes.* Necrosis of non-dividing spermatocytes of the first order can be detected three or four days after exposure. Between the third and ninth days, large necrotic masses appear. After the ninth day they disappear, presumably by being washed away into the lumen of the tubule by discharge of fluid. This necrotic change can be seen in unstained specimens, but much more readily in stained ones, since basic dyes are readily taken up, while acid dyes are without effect. If necrosis has not progressed so far as to make detailed examination impossible, other changes may be detected. Such are contraction of the nucleus, disappearance of the nuclear membrane, the spireme stains badly, and is contracted into one or more portions.

When necrosis attacks a spermatocyte of the first order which is undergoing mitosis, darkly-staining masses may be seen; these are altered chromosomes.

(2) *Non-necrotic changes.* These are various and among the most frequently met with are: enlargement of the clear space surrounding the intranuclear body, formation of intranuclear vacuoles independent of the intranuclear body, and thinning of the spireme. This last phenomenon is sometimes associated with necrosis.

Other changes are multipolar mitosis and abnormal bipolar mitosis. Multipolar mitoses are observable only at the end of twenty-four hours after exposure; the number of spindles varies from two to four. Common poles, varying in number

from one to three, may also occur, the mitotic figures produced under these conditions being manifestly difficult of analysis.

Abnormal bipolar mitoses are also seen at the end of twenty-four hours. The chromosomes are more numerous and smaller than normal; they are often collected to one side of the spindle, and one or more may lie free in the cell unattached to any spindle fibres.

(*e*) *Spermatocytes of the second order.* These cells are relatively inconspicuous and few in number, and so are difficult of observation. They disappear about five days after exposure, but the method of their disappearance is uncertain; the only change noted prior to their complete disappearance is amitosis.

(*f*) *Spermatids.* Young spermatids may undergo necrosis either before or during the formation of the head. The phenomenon was first noted on the fourth day after exposure, and was marked by the ninth day. The fatty change which normally accompanies the formation of spermatozoa is markedly increased between the fourth and ninth days.

(*g*) *Spermatozoa.* The only change appears to be softening, which is manifested by the separation of the filaments.

(*h*) *Abnormal forms due to X rays.* Two structures, which cannot be definitely referred to any of the cell constituents of the normal testes, are seen after exposure to the X rays; these are multinucleate and multivacuolate cells. The multinucleate cell masses are the less common; they were detected on the third day after exposure, but rapidly disappeared. Their size may be either greater or less than that of a spermatocyte of the first order.

The multivacuolate forms, commoner than the preceding, occur between the fourth and seventh days. The vacuoles may number from two to twelve, and their diameters vary from 4μ–12μ.

A careful study of the effect of X rays upon the mitotic figures of certain cells of the testicle was made by Amato in 1910. He selected the frog as the subject of his experiments, and as mitotic figures preponderated in the spermatogonia and spermatocytes of the first order, the observations were limited to those cells.

Single exposures of 30 minutes were given, the abdomen of the animal being 18 cms. from the anti-cathode.

As regards the resting cells, the changes consequent upon

irradiation appear to be vacuolation, and but little of anything else. This vacuolation generally occurs in the centre of the cell, the nucleus consequently being thrust to one side. In cases where the centrosome is visible, it and the nucleus occupy different sides of the large central vacuole. At other times the change takes the form of a marked rarefaction of the cytoplasm in the perinuclear zone, so as to present the appearance of a nucleus lying in a large vacuole with a condensation of the cytoplasm at the periphery of the cell. Fragmentation of the chromatin also occurs; at first the little chromatin masses are scattered throughout the nuclear substance, but subsequently become arranged at the nuclear periphery. At other times there is rupture and disappearance of the nuclear membrane with scattering of the chromatin granules through the cytoplasm; or, again, in cases where there has been a central perinuclear rarefaction of the protoplasm, this rupture and disappearance of the nuclear membrane give a picture of a central vacuole containing chromatin fragments. A further phenomenon which is sometimes observed is the fusion of the chromatin fragments into three or four relatively large masses within the still persisting nuclear membrane. This condensation and fusion of chromatin, which, as seen, may be produced in the resting nucleus, is however, especially characteristic of nuclei undergoing mitosis.

Regaud submitted the testicles of cats to doses of X rays in a manner similar to that already described in the case of rats. He was able to show certain differences, however, in the two cases, and directs attention to a type of cell to be found in the generative layer which is very resistant to the X rays. These particular cells resemble those to be found in the seminal epithelium of all sexually immature mammals, but which apparently persist in the adult cat. Regaud remarks that it is more difficult to sterilise cats than to do so in rats.

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OVARY.

In 1905 Halberstädter first noticed atrophic changes in the ovaries of rabbits as a sequel to irradiation by X rays. On one side the ovary was protected by a lead screen, the other ovary being unscreened ; the exposures were of thirty minutes' duration, the average doses being 6–8H. After a few days the exposures were repeated, and the animals killed from ten days to three weeks afterwards. The irradiated ovaries were invariably found to be smaller than the normal organs. Microscopically there was almost complete disappearance of the Graafian follicles. As early as the tenth day after exposure these were found to be diminished in size ; by the fifteenth day they had almost completely disappeared. A striking histological feature was the presence of a number of clearly-defined spaces without any definite epithelial lining, and which contained eosinophile débris. Such structures are indeed found in normal ovaries, but in much less numbers. The corpora lutea showed no change.

Similar observations on the destructive effects of the rays upon the ovaries of rabbits were made by Bergonié, Tribondeau and Recamier. By irradiating them for different periods they found that the loss of weight was more marked with increased duration of exposure, thus :

An ovary irradiated for	60	minutes lost	42	per cent.	of its weight.
,, ,,	80	,, ,,	30	,,	,,
,, ,,	120	,, ,,	30	,,	,,
,, ,,	140	,, ,,	85	,,	,,

The ovary irradiated for 140 minutes was found to be completely deprived of the Graafian follicles when examined one month after the exposure.

Results broadly confirmatory of Halberstädter have also been recorded by Specht, Okintschitz, Roulier, Fränkel and Lengfellner.

Saretzky found the ovaries of rabbits very susceptible to the

rays, and that the most sensitive parts of the ovary were the maturing and matured follicles.

Krause and Ziegler irradiated mice for six hours, using a hard Muller tube, distant 20–40 cms. from the animals, which were killed 24 hours afterwards. Numerous follicles were found in different stages of maturity. The cells of the zona pellucida



FIG 42.



FIG. 43.

FIG 42.—*Ape* Irradiated ovary, showing degeneration of primary follicles. The ovum cells are reduced to a mere débris, the follicular epithelium showing indefiniteness of cell outline, with badly staining or completely degenerated nuclei. The larger follicles are often disintegrated and filled with hyaline débris

FIG. 43.—Control ovary.

were found to be desquamated; some were necrotic, and the ovum itself floated among these cells in the liquor folliculi.

Reifferscheid (1910) irradiated mice, bitches and monkeys, and in all cases observed retrograde changes as a consequence. Details of the normal appearance of the ovary are given by Reifferscheid in the case of the mouse, and by Simon, whose work will be considered later, for those of the guinea-pig and bitch.

In addition to his animal experiments, some of the results of

which are illustrated in Fig. 42 and Fig. 44, Reifferscheid gives an account of the changes occurring in the human ovary as a sequel to irradiation by the X rays. Six cases are recorded by him, in which, after unsuccessful treatment by X rays, operative measures were undertaken. A synopsis of results is given in Table 50, which shows a remarkable similarity in the general



Fig 44.

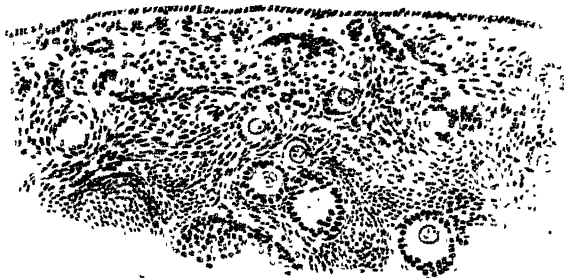


Fig. 45.

Fig. 44.—*Fox-terrier bitch.* Irradiated ovary, showing destruction of the follicles with disappearance of ovum cells throughout.

Fig. 45.—Control ovary.

trend of the changes brought about by exposure of the ovary to the rays.

Later observations upon the ovary are those of Simon, who investigated the effects of the X rays upon this organ in the guinea-pig, rabbit, bitch and the human subject. His findings are in conformity with those of Reifferscheid, and as they present a good résumé of the question, will be considered in some detail.

TABLE 50.

No	Age	X ray dose	Removal of ovary.	Histological findings.
1	52	½ erythema dose, spread over several days.	1 day after last application.	Senile atrophy of ovaries, in which only the remains of follicles were found; also small capillary hæmorrhages.
2	40	½ erythema dose, spread over 16 days.	10 days after last application.	Small number of primary follicles in degenerative condition; the ovum had shrunk into a hyaline mass. Partial destruction of follicular epithelium with capillary hæmorrhages.
3	37	1¼ erythema doses, spread over 22 days.	18 days after last application.	Loss of outline of the cells of the epithelium of primary follicles, which were few in number; the large follicles suffered almost complete destruction. Disseminated capillary hæmorrhages.
4	39	1 erythema dose, spread over 11 days.	9 days after last application.	Numerous primary follicles in all stages of degeneration. Partial destruction and loss of outline of epithelium of the larger follicles. Small hæmorrhages in peripheral portion of the ovary.
5	35	½ erythema dose, 1 application.	4 days after application.	Partial degeneration of epithelium of both the primary and mature follicles; hyaline change of ovum, with capillary hæmorrhages in peripheral zone of ovary.
6	36	½–1 erythema dose; 2 sittings	3 days after last application.	Primary follicles diminished in number, and showing all stages of atrophy. Analogous changes in epithelium of mature follicles.

(*a*) *Ovary of the guinea-pig.* The animals were placed upon their backs, the X-ray bulb being 20–30 cms. away, and having a hardness of 4–6 upon Walter's scale.

Guinea-pig I. Dose 10X (Kienböck). Killed 12 hours after exposure. At this stage there were quite definite changes in the ovum and in the epithelium of the follicles. In the primary follicles the ovum cell had mostly disappeared and its situation was indicated merely by a hyaline residium. In the more matured follicles the ovum cell also showed different degrees of advanced degeneration. In the stroma of the ovary were numerous small stellate hæmorrhages; but, with this exception, neither it nor the "corpora lutea" showed any changes.

Guinea-pig II. Dose 12X (Kienböck). Killed 4 months later. In this case the degenerative processes were of a more profound character. The follicular epithelium was, in places, entirely gone; where cells still persisted, their nuclei were degenerate and the cell outlines indistinct. The ovum cell was in general represented merely by a hyaline spot. In the whole section not a single normal follicle could be seen.

The whole ovary was hyperæmic; the stroma cells had a swollen and glassy appearance, and stained indifferently.

(*b*) *Ovary of the Rabbit.* The animal was irradiated as before. Dose 8X (Kienböck). Duration of exposure, 1 hour. One month after irradiation the right ovary was removed. Eighty-two days after this operation, the second ovary was removed and examined.

Ovary I. The organ was found to have undergone severe damage. In the primary follicles the ovum cells had entirely gone, or were merely represented by the hyaline globule previously referred to; the epithelium of the follicles had also disappeared. The mature follicles similarly showed degeneration in ovum and epithelium. The cells of the stroma were also found to be damaged, their outlines were indistinct, and the nuclei stained badly.

Ovary II. In this ovary, removed 82 days after the first, the degenerative changes had proceeded still further. The corpora lutea, however, showed no evidence of having been affected by the rays.

(*c*) *Ovary of the bitch.* Two animals were irradiated.

Animal No. 1. Duration of exposure, 1 hour. Dose 8X (Kienböck). One ovary removed 6 days after irradiation, the second removed three months after the first.

Ovary I. Six days after exposure there was marked hyperæmia of the whole organ, numerous hæmorrhages being observed in the stroma and also into the follicles. The follicular epithelium showed pycnotic nuclei and the cell outlines were indistinct. The ovum cells underwent the degenerative changes previously mentioned and in some cases had entirely disappeared.

The primary follicles were often only represented by spaces containing a little ill-staining débris. At the same time, however, fair numbers of follicles were observed which showed no deviation

whatever from the normal. The stroma exhibited no changes except local hæmorrhages.

Ovary II. Removed three months later. Numerous corpora lutea present, apparently from two to three weeks old; their component cells were of normal appearance. In the Graafian follicles, however, the changes were more advanced than in the ovary examined three months previously. A follicle could rarely be seen which was normal in appearance. A histological examination of the uterus showed sexual activity, characterised by blood extravasation under the mucosa and enlargement of the uterine glands.

Animal No. 2. Two irradiations were given on two consecutive days. Total dose 16X (Kienböck). The animal soon showed depilation and well-marked X-ray dermatitis. One ovary was removed three weeks after irradiation and the second 68 days later.

Ovary I. The follicles showed very marked degeneration. There was vascular engorgement, but only here and there were to be seen indistinct evidences of blood extravasation and in these cases the red-blood cells were already degenerate.

Ovary II. Very extensive hæmorrhage had taken place in the ovarian tissue and large numbers of follicles had become cystic. In the membrana granulosa such cells as remained were degenerated and extravasation of blood had occurred among them. In addition to the follicles, which had become cystic, were others of small size, in which cellular destruction was the predominant feature. No normal follicles could be seen and the general histological appearance was one of complete atrophy of the organ. The stroma cells were much reduced in numbers; the few which remained stained badly and their outlines were indistinct.

(*d*) *Human ovary.* The specimen was obtained from a woman aged 42 years, who had received a total irradiation of 30X (Kienböck) on account of menorrhagia and dysmenorrhœa. As this treatment was ineffectual, supra-vaginal amputation of the uterus was performed, with removal of the right ovary. This showed a few small hæmorrhages and, considering the patient's age, contained very few follicles and in those which were present, degenerative changes had begun. The changes were similar in character to those described for the ovaries of the lower animals,

atrophy of the follicular epithelium and disappearance of the ovum cell. No evidence of regeneration was found in any of the ovaries examined.

LAW OF BERGONIÉ AND TRIBONDEAU.

From extensive studies upon adult and embryonic cells, and upon cells in a state of rest or of active division, Bergonié and Tribondeau were led to the following generalisation which is known as the Law of Bergonié and Tribondeau : Immature cells, and cells in an active state of division are more sensitive to the X rays than are cells which have already acquired their fixed adult, morphological or physiological characters.

It fittingly finds a place here, inasmuch as many of the cytological studies upon which it was based, were made upon the testicle of the rat.

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RADIUM.

Horowitz observed atrophy of the Graafian follicles in the ovary of a rabbit after its irradiation for 10 days by 1 mgr. of radium bromide.

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CHAPTER XVI

MALIGNANT CELLS

RADIUM.

THE tumours occurring in mice and rats, which are freely transplantable by the simple process of subcutaneous inoculation, afford good material for the study of the effects of the rays upon malignant cells. One function of these cells, namely that of progressive growth when inoculated into a normal mouse or rat, can be accurately observed in a way which is scarcely possible with the ordinary tissues of the animal body; this function of growth appears, moreover, to be so easily influenced by the rays in question, that the failure of malignant cells to grow when inoculated may be the only detectable indicator that any change has occurred in the cells as a result of the irradiation. When a tumour, situated for example, in the axilla of a mouse, is exposed sufficiently long to the rays from radium, the result is frequently that it undergoes a rapid absorption.

Apolant, in 1904, was one of the first observers of the effect of the rays from radium upon tumours in mice. Irradiation of the tumour *in situ* resulted in many cases in its subsequent disappearance. The exposures were carried out with 20 milligrams of radium bromide applied to the surface of the tumour, 10 to 12 days after the inoculation of a graft; the radium preparation was covered with mica, so that the effects obtained were probably due to the beta rays. Two carcinomatous varieties of tumour were observed under these conditions with adequate controls; out of 19 tumours treated for varying periods of time, 11 disappeared and a diminution occurred in the remaining 8. Of the 17 control tumours, 2 suffered spontaneous absorption, the

remaining 15 showing progressive growth. Apolant concluded, on histological grounds, that the destruction of the carcinoma cells was not a sequel to the proliferation of the connective tissue cells, but that it was due to a direct action of the rays upon the parenchyma.

The general trend of such observations was soon afterwards confirmed by Bashford, Murray and Cramer, who exposed Jensen's mouse tumour to 10 milligrams of radium bromide for varying periods of time, the result of which was, not infrequently, that the tumour diminished in size and subsequently disappeared. Histological examination of such tumours in the process of disappearing showed that there was a marked proliferation of the connective tissue, which splits the tumour up into small islands of cells ; no abnormalities were, however, seen in the tumour cells which had been irradiated. The observation was made that hæmorrhages were a very frequent sequel to the exposure of the tumours to radium ; this fact, together with the histological findings referred to, led Bashford, Murray and Cramer to the view that the disappearance of the tumour was not due to a direct action of the rays upon the malignant cells, but that it was a sequel to the hæmorrhages and the induced connective tissue proliferation.

This may indeed be the case when the tumour is irradiated in the animal's body ; but if the tumour be excised and then irradiated, the experimental work of Wedd, Chambers and Russ has shown that inoculation of such irradiated material into mice or rats will not produce tumours ; hence the radiation causes some change or changes to be set up in the malignant cells, which prevent their subsequent progressive growth ; the nature of such changes is, however, still obscure.

A few details of these *in vitro* experiments will be given, as the method may be of service in determining the relative sensitiveness of different types of malignant cell to the rays. A series of experiments with an adeno-carcinoma (Twort) of the mouse was made as follows : a thin slice of tumour about 2 mms. thick was placed between two sterilised sheets of mica ; the tumour was moistened with normal saline and enclosed by a vaseline ring, which prevented evaporation. This was placed between two radium capsules, giving an intensity of radiation equal to 2.2 milligrams of radium bromide per sq. cm. An initial exposure,

lasting four hours, to the composite rays from the radium prevented the subsequent growth of the tumour when it was transplanted into five mice, a control portion of the original tumour "taking" in all of the inoculations. The small penetrating power of the alpha rays (about .1 mm. of the tumour) rendered it unlikely that they were the cause of this effect. When these rays were eliminated by a thin mica screen (.1 mm. thick), an exposure of half an hour was just as effective in inhibiting growth as when the alpha rays were included, as may be seen from Table 51. By interposing lead screens 2 mms. thick between the radium and the tumour, the beta rays were eliminated, the gamma rays alone operating. In this case an exposure of 18 hours was insufficient for any decided inhibitory action. The data show that the beta rays were mainly responsible for the effect upon the growth of the tumour when transplanted.

TABLE 51.

Character of Rays.	Time of Irradiation.	Number of Mice.		Growth of Tumour.	
		Inoculated.	Survived.	Positive	Negative.
α, β, and γ-rays	15 minutes	6	4	2	2
	30 ,,	6	4	3	1
	4 hours	5	3	0	3
β and γ-rays	30 minutes	14	10	6	4
	1 hour 30 mins.	8	4	0	4
	2 hours	6	4	0	4
	4 ,,	12	9	0	9
	Controls	37	29	18	11
γ-rays	$3\frac{1}{2}$ hours	8	7	3	4
	Controls	8	7	4	3
γ-rays	18 hours	6	6	2	4
	Controls	6	6	3	3

An exactly similar procedure for the Jensen rat sarcoma gave the results depicted in Fig. 46. It will be seen that, as a result of irradiation for 30 minutes, there is a slower growth of the irradiated than of the untreated tumour when the inoculations are made into the same rat. When the period of irradiation is increased to 90 minutes, the inoculated material, although

apparently increasing in size for some days, was eventually absorbed in the animal, which was simultaneously supporting the growth of the control tumour; extension of the period of irradiation to three hours ensures the progressive and complete absorption of the tumour cells.

Exposure of an emulsion of these malignant cells to radium emanation may in a similar manner prevent their growth when inoculated into animals. If the exposure be not too prolonged, there is a delayed onset of growth when the cells are inoculated, and it is interesting to find that the rate of growth of the tumours

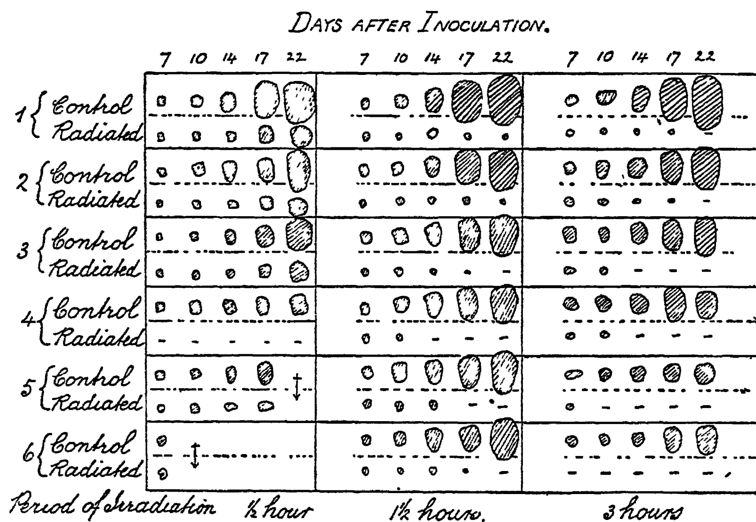


Fig. 46.

resulting therefrom is markedly less than that of the normal tumour. By exposing an emulsion of Jensen's rat sarcoma to .275 milli-curie for 30 minutes and inoculating the emulsion, tumours grew, but very slowly, actually about one-third of the normal rate, and by successive transplantations from this slowly-growing tumour for more than a year, the tumour was still found to be growing at about one-third of the normal rate; this persistence of a lowered rate of growth is analogous to the persistence of new histological characters imposed upon a tumour by X rays (*vide* p. 300).

Tumour cells therefore, if irradiated outside the animal, may

be given an accurately measured quantity of beta rays, so that when the cells are re-inoculated, they will not produce growing tumours. The inoculated cells persist for a few days, then undergo absorption; such irradiated tumour cells can in certain cases induce an immune condition in the animal into which they are inoculated, for Wedd, Morson and Russ have shown that, in the case of the Twort tumour, if the irradiated cells were inoculated into mice, the animals were immune when inoculated some days later with the normal strain of tumour. The degree of immunity conferred gradually decreased to zero as the exposure of the cells to the rays was prolonged; it may be noted that Haaland was also unable to detect any immunity in mice which were inoculated with carcinoma cells which had received a prolonged exposure to radium.

The consideration of some immunity process being called into play by malignant cells after irradiation has an evident interest in connection with radium-therapeutics. It is a frequent clinical practice to insert platinum tubes containing radium into malignant growths and in some cases the growths have been observed subsequently to disappear, the cells which have been irradiated being gradually absorbed into the body; whether they have given rise to a condition of immunity is clearly of significance. It is impossible to generalise from the limited amount of experimental work that has been done in this direction, but the indications appear to be that an excessive amount of irradiation of the malignant cells may abolish any immunity that such cells may be capable of giving rise to. It would appear that the best condition for producing such immunity is for the cells to receive an exposure which will just ensure their gradual degeneration and disappearance.

The fact that carcinoma or sarcoma cells may be removed from an animal and be given a measured quantity of beta rays, sufficient to ensure that such cells will not develop into tumours if re-inoculated, was used by Price-Jones and Mottram to decide a question which has arisen in connection with *in vitro* cultures of malignant cells. According to the procedure of Carrel, a small piece of the tissue is taken and cultivated in the plasma of the animal, due regard being paid to a rigid asepsis in the process; if the fragment of tissue be kept at 37° C., it increases in superficial area to a considerable extent and the question occurs, is

this enlargement of the tissue a real growth such as division of the cells would produce, or is it merely a spreading of the cellular elements constituting the initial fragment? The method they adopted for deciding this question was to prepare a large number of such cultures, then to submit a portion of them to a quantity of beta rays sufficient to ensure that no proliferation of the cells would occur; the cultures were then observed along with the controls under identical conditions, leading to the following conclusions: "Growth of *in vitro* cultures consists of two processes: (*a*) a spreading of area of the original mass by the exten-



FIG 47.—"In vitro" culture of Jensen rat sarcoma, illustrating the spreading growth after being exposed to beta rays.

sion of cells possessing long, often branched, amœboid processes, (*b*) a division of cells by mitosis; and the spreading may occur quite independently of mitosis. Whereas radiation with a 7 mg. capsule of radium bromide for periods of time ranging from 2½ to 18 hours has no retarding influence on the 'spreading growth,' it has a marked inhibiting effect on mitosis (*vide* Table 52). It would seem therefore that an increase in superficial area observed in an *in vitro* culture must not necessarily be regarded as growth in the sense of a multiplication of cells by mitosis."

Fig. 47 illustrates a typical "spreading growth" after being irradiated.

TABLE 52.

	"Takes."	
	Irradiated	Non-irradiated.
Mouse carcinoma (74 cultures) -	66 per cent.	78 per cent.
Rat sarcoma (198 „) -	80 „	68 „
	Mitoses	
	Irradiated.	Non-irradiated.
Mouse carcinoma (20 cultures stained)	0 ?	0 ?
Rat sarcoma (68 „ „)	3 ?	307

It has been previously mentioned that, subsequent to irradiation, the failure of growth of grafts of a carcinoma or sarcoma is often the only indication that any change has been brought about by the rays; histological changes require time for their development and if irradiated portions of a tumour be put into a mouse or rat and removed some days later, such changes may be recognised; they are in general of a degenerative character, consisting of an enlargement of the cells, some of which may be multi-nucleated, or exhibit a diffuse nuclear staining. Tworts' mouse carcinoma shows some of these changes after having been exposed to comparatively small quantities of beta rays. The cells of this carcinoma exhibit Altmann's granules, and in view of Beckton's finding that such granules may disappear in normal tissues if exposed to radium emanation, Miss Lepper investigated the behaviour of these granules in grafts of the carcinoma. The grafts previous to inoculation had been exposed to beta rays sufficiently long to ensure their gradual disappearance, instead of progressive growth; during this period of about a week, she observed that the cells retained their granules with no apparent diminution in number; this observation indicates that the granules are a rather stable feature of the cell content.

The action of the rays from radium upon malignant cells is a complex one; that malignant tumours in man have been observed to disappear after exposure to the rays is undoubted and from this simple but pregnant fact a knowledge of the mechanism by which it is effected must spring. That essentially different

processes are set in train in the various types of malignant cells when they are exposed to the rays from radium is already apparent, but if a malignant mass, for example a sarcoma, be exposed to beta rays or to gamma rays, either of which may cause its disappearance, we do not know that the intra-cellular processes provoked are the same under these two different conditions.

Dominici has made an extensive study of the processes which are involved when the disappearance of malignant tumours is brought about by the hardest gamma rays; by his method of excluding all beta and soft gamma rays by screening with 3 mms. of lead, a valued degree of precision is introduced. That a destruction of the malignant cells occurs as a direct result of the irradiation is no doubt in some cases true, but Dominici submits considerable evidence to show that this is by no means always the case, or indeed necessary for the ultimate resolution of such cells.

Histological changes induced in malignant cells by very minute quantities of radium are recognisable, if the exposure to the weak radiation is sufficiently prolonged; the effect of the rays from pitchblende (about a million times weaker than a corresponding quantity of radium) upon skin nodules, secondary to a mammary carcinoma, was studied by Hastings, MacCormac and Woodman; after the lapse of several months, although no clinical evidence of any change was apparent, histological examination of a number of the irradiated nodules showed recognisable differences from nodules receiving no rays; these differences were twofold: (1) the malignant cells appeared to be separated from one another by fine fibres of connective tissue, fibroblasts becoming more numerous; simultaneously with the gradual separation of the cancer cells into small masses, nuclear changes appear in them—a marked feature being the partial disappearance of chromatin and its local condensation about the nuclear membrane; (2) a tendency on the part of the cancer cells to arrange themselves at the periphery of the nodules, parallel to the skin surface. It is interesting to compare this last finding with that of Dominici, who observed a similar phenomenon in the case of irradiated normal skin of the guinea-pig (p. 179) and also in the scar tissue resulting from the regression of certain malignant growths after irradiation (p. 292).

Dominici, Rubens-Duval, Barcat and Faure-Beaulieu have made an exhaustive series of studies upon the histological changes

accompanying the regression of malignant growths after exposure to radium. The ultimate result in such a case, after successful exposure, is the disappearance of the malignant neoplasm and its replacement by a relatively small amount of fibrous tissue. At first sight it might appear probable that such a result was attained by the destruction of the malignant cells, followed by ordinary cicatrisation. According to these authors, however, this is not the case, and their researches lead them to the conclusion that



FIG. 48.—I. Section of sarcoma prior to irradiation Magnification 97 diameters. Dominici, *Archives de Médecine Générale*. 1909.

the malignant cells themselves undergo progressive changes, resulting in their conversion into cells which are indistinguishable from normal connective tissue cells. In the case of lymphadenomata and carcinoma this evolution is admittedly difficult to establish; with sarcomata, on the other hand, the changes are plain and capable of easy demonstration.

A sarcoma described by Faure-Beaulieu and Dominici (illustrated in Figs. 48, 49, and 50) will serve as an example of this process. The growth sprang from the gum of the upper jaw in the situation formerly occupied by the left canine tooth

(which had been lost from dental caries some fifteen years previously) and made its appearance about three months prior to the commencement of treatment. Histological examination, made before irradiation was undertaken, revealed a typical myeloid sarcoma of a very vascular character. The treatment was commenced on the 12th September, 1908, and by the 20th January, 1909, the growth had entirely disappeared and was represented solely by a small fibrous scar. The changes accom-



Fig. 49.—II. Section of the same tumour ninety days after the commencement of radium treatment. The greater part of the field is occupied by fibrous tissue, while the sarcomatous elements are reduced to isolated islands of cells. Magnification 97 diameters.

Dominici, *Archives de Médecine Générale*. 1909.

panying this regression of the tumour may be summarised in the three following groups :

(1) The metamorphosis of a part of the protoplasm of the giant and other cells of the sarcoma into connective tissue fibres.

(2) The conversion of the rest of the cytoplasm and of the nuclei of the sarcomatous elements into connective tissue cells.

(3) The obliteration of the large blood spaces of the sarcoma.

The nuclei of the sarcoma cells, originally oval or round in outline, undergo marked elongation, while at the same time atrophic changes are also distinguishable. The protoplasm of

the giant cells and of the other sarcoma cells is replaced by connective tissue fibres, which are the product of their transformation; in the immediate vicinity of the nuclei, however, a part of the cytoplasm persists, to form with them typical adult fixed connective tissue cells. This occurs not only in the intervascular portions of the growth, but extends up to the very margins of the blood channels, which consequently undergo a marked diminution in lumen and acquire the characteristics of capillaries, with their flattened and elongated endothelium. The vessels

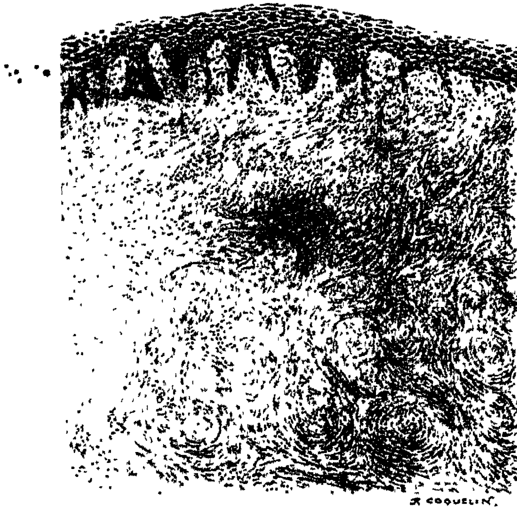


FIG. 50.—III. Section of the same tumour after conclusion of the treatment. The malignant cells have entirely disappeared, and the section resembles that of a fibroma Magnification 97 diameters.

Dominici, *Archives de Médecine Générale*. 1909.

however, do not lie in a mass of sarcoma tissue, but in tissue which shows the characters of a fibroma.

The general conclusions reached from these observations are, that the irradiation has determined the transformation of a malignant into a benign neoplasm (fibroma). The fibroma, moreover, does not tend to increase in size, as is usually the case even with benign growths, but to remain stationary or to actually diminish in size. This diminution is due to progressive atrophy of the cells, with coincident concentration of the fibrous tissue, together with diminution in the calibre of the blood-vessels. The general trend of the whole process is towards the formation of a cicatricial

fibrous plaque, of remarkably regular structure and with its surface even with the rest of the mucous membrane of the mouth.

In the case of carcinomata, Dominici and Rubens-Duval describe the action of radium as depending upon the destruction of certain of the carcinoma cells and the arrest of proliferation of the remainder.

The destructive action may be direct or indirect. In the case of direct destruction, the neoplastic cells are killed without any obvious morphological change. In indirect destruction, on the contrary, the death of the cell is preceded by definite alterations in structure; these are as follow:—

(1) Hypertrophy of cell-body and nucleus.

(2) Nuclear budding.

(3) Increase both in size and in number of the "pseudo-parasitic" bodies.

Squamous cell carcinomata, in addition to these changes, exhibit keratinisation as a sequel to irradiation.

The following is an abstract of the changes produced in a carcinoma of the breast, as described by Dominici and Coyon.

Macroscopically, the growth was ulcerated and superficially necrotic, occupying an area of some 80 square centimetres. It was markedly indurated and obviously adherent to the subjacent pectoral muscle.

The growth was subjected to irradiation by the screened rays, the apparatus being left in place for seventy hours. Three or four days after, the surface was the site of a serous discharge which lasted about three weeks and was followed by disappearance of the gangrene and the formation of clean granulations. One month and a half after the exposure to radium, recuperative processes appeared and eventually half the originally ulcerated surface was healed. The subjacent tissues, originally indurated, gradually became more supple. Three months after the commencement of treatment the growth was reduced to one-half of its original dimensions and this not only on the surface, but also in the deeper parts. The treatment was about to be resumed when the patient died of an intercurrent disease—bronchitis. At the autopsy no metastases were discerned, but the breast was removed for further examination. Beneath the cicatrised part was found a layer of normal fatty tissue in place of the pre-existing cancerous growth; the connection of the tumour with

the pectoral muscle was in process of disappearance, infiltration of the muscle by the malignant growth being only in localised patches, and even then the muscle tissue was invaded only to the depth of one or two millimetres.

The portion of growth which remained after treatment showed marked deviations from the non-irradiated type; the changes were :—

(1) Marked increase in the connective tissue and diminution in the number of cancer cells.

(2) The transformation of the spheroidal carcinoma cells into large cells with a budding nucleus in process of disintegration. Although the majority of the cancer cells which still persisted showed these degenerative changes, a few were found which still preserved the normal morphological characters of carcinoma cells.

The preceding affords a fair example of the regression of a malignant growth by indirect cell-destruction, and without keratinisation.

In squamous cell carcinomata, this indirect cell-destruction may be, as stated, accompanied by well-marked keratinisation. Dominici and Rubens-Duval drew attention to three cases of this type; one of these was a carcinoma of the cervix uteri, the remaining two of the lip.

In the case of the uterine carcinoma, three exposures, each of twenty-four hours' duration, were given at intervals of one month. The amount of radium bromide used was 50 milligrams, enclosed in a glass tube; this in turn was placed in a silver tube, half a millimetre in thickness and the whole enveloped in rubber, which in turn was two millimetres thick. The apparatus was placed in the cervical canal, and fifteen days after the last application, hysterectomy was performed. On examining the specimen, the whole of the cervix uteri presented the typical characters of squamous cell carcinoma, with the exception of a zone one and a half centimetres in diameter, which surrounded the central canal in which the radium tube was lodged. In this region the carcinoma cells had undergone degeneration and hyperkeratosis. This was accompanied by loss of vitality of the cells and their subsequent ingestion by phagocytes, after the manner of any other non-living and relatively inert bodies.

In the cases of carcinoma of the lip, the changes consequent upon irradiation were not at first sight so obvious. Closer examin-

ation however, revealed the fact that there was an increase, both in size and numbers, of the keratin granules. Eventually the whole nodule of new growth became transformed into keratinised masses, at the periphery of which no unchanged cancer cells could be distinguished. These keratinised masses, deprived of their vitality, cause a reaction on the part of the surrounding connective tissue; the connective tissue cells, reinforced by the accession of mononuclear lymphocytes, adapt themselves to phagocytosis on a large scale, by fusing to form phagocytic plasmodia, or giant cells. The keratinised layers are little by little eroded and digested by these plasmodia and cells, polynuclear cells sometimes assisting in the process of demolition.

The hyperkeratosis is preceded by a hypertrophy of all the cell elements, cytoplasm, nucleus and nucleolus. The enlargement is specially marked in the case of the nucleus, which stains unusually deeply, becomes lobulated and shows signs of budding. These nuclear abnormalities are however, according to Dominici and Rubens-Duval, always less pronounced in squamous cell carcinomata than in growths of glandular type.

The rapid maturation of the epithelial cells under the influence of radium differs from the normal, by the excessive development of eleidin and keratin. Eleidin is produced in marked excess and forms large spherules; the appearance of this eleidin is followed by keratinisation of the cell. The keratinisation may be complete; in which case the nucleus disappears and the whole cell is reduced to a homogeneous horny mass. More usually however, the nucleus persists, becoming pycnotic and forming a compact mass of chromatin in the midst of the keratinised mass. The appearances are very much like those described by Darier and Menetrier as the result of the exposure of normal skin to X rays.

Observations upon the histological changes consequent upon irradiation of malignant growths by radium have also been made by Morson. In all cases the platinum tube containing the radium was imbedded in the tumour and left *in situ* for periods varying from fifteen to twenty-four hours. Portions of the growth were removed for examination at periods between twenty hours and two months after exposure. One circumstance attending the removal of these specimens is noteworthy; there was complete loss of sensation in the irradiated parts, so that no anæsthetic was necessary.

Within fifteen hours of the commencement of irradiation,

histological changes were sometimes manifest; the cells in the immediate vicinity of the radium tube exhibited signs of degeneration, their nuclei showed irregularity of contour and in some cases fragmentation. Twenty-four hours later the sections showed an apparently structureless mass, in which were embedded cells in various stages of degeneration. These conditions are well seen in Fig. 51 and Fig. 52.

In many cases specimens examined within fourteen days of the exposure to radium showed no sign of cancer cells. It must, however, be borne in mind that this is by no means invariably

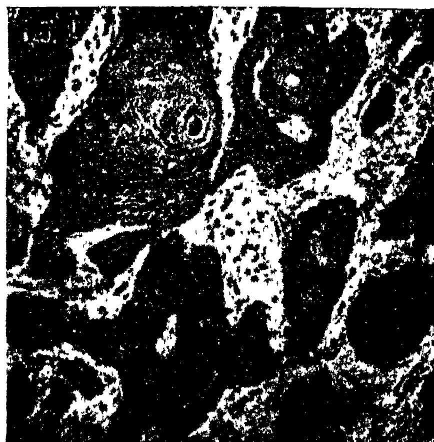


Fig. 51.—Squamous cell carcinoma of upper lip; appearance before exposure to the gamma rays.

the case; in some specimens examined two months after irradiation, malignant cells could still be detected, although their nuclei were swollen, their cytoplasm vacuolated and they were surrounded by dense fibrous tissue.

A suggestion having been made that the changes previously described were not due to the radium but to some effect of the metal tube containing it, Morson performed a control experiment. A silver tube 2.8 cms. long, containing 40 milligrams of radium bromide, confined to one end, was inserted into a recurrent mammary growth for twenty-four hours. The tract of tissue lying along the whole length of the tube was then excised, and upon examination, it was found that the carcinoma cells in the

immediate neighbourhood of the radium showed degeneration, while those in contact with the other part of the tube were unaltered.

Finzi has drawn the conclusion, based upon clinical experience, that when radium is applied to a malignant growth which is the seat of sepsis, the septic condition will be improved if the reaction of the growth to the radiation is a favourable one; but that a worse condition will supervene if this reaction is an unfavourable one. The septic condition, may, as Finzi states, improve or it may not, and there is little doubt that clinical results would

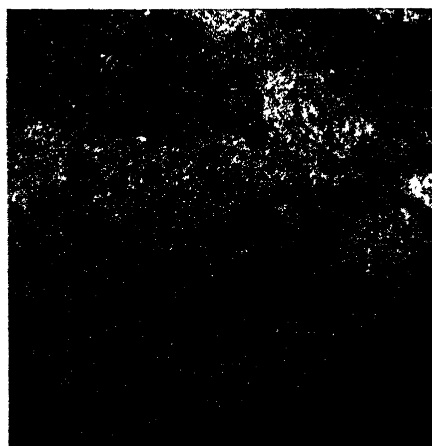


FIG. 52.—Appearance of growth forty-eight hours after commencement of treatment with 90 mg of radium bromide. (Same magnification as Fig. 51.)

be more certain if better means could be found for dealing with the complicating septic conditions. It does not seem irrational to attribute some part to the normal tissues of the host in what is called the reaction to the radiation given, and it is highly probable that this would be influenced by a septic complication.

Knox has directed attention to the essentially different reaction subsequent to the use of beta and of gamma rays, and he submits that when necrosis of a malignant growth is desired, recourse should be had to the beta rays.

The administration of the type and intensity of radiation most appropriate to any particular malignant growth is a matter of

great difficulty, and although the data may at present be insufficient for any sure basis of radium-therapy, yet a large number of facts are being gleaned which should render this possible in the near future.

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X RAYS UPON MALIGNANT CELLS.

Contamin has exposed tumours in mice to X rays under various experimental conditions and records some interesting results. The tumour selected was a carcinoma of glandular type ; the mice bearing the tumours were placed at a distance of 12 cms. from

the anode of a bulb running at 9–12 cms. spark gap, the rays being filtered through .2 mm. of aluminium. Tumours as large as the mice bearing them were eventually seen to disappear after they had received an exposure of 1 hour. Tumours in a stationary condition were not affected in any way by such treatment. As a result of a number of observations Contamin came to the following conclusion:—

(1) The action of X rays is the greater, the younger and more actively growing the tumour is.

(2) The disappearance of a large tumour causes the death of the animal, probably by intoxication.

The disintegration products of the cells which have been injuriously affected by the rays are eventually absorbed by the body; in the case of excessive quantities this leads to a state of intoxication.

Nogier, Jaubert de Beaujeu and Contamin have shown the direct effect of X rays upon the cells of a mouse tumour (*B*), an epithelioma of glandular type (adeno-carcinoma).

The tumour, upon removal from the animal, was minced and then exposed to X rays, after which it was inoculated into normal mice to see whether it would grow. A typical example, showing how the subsequent growth is interfered with, is reproduced in Table 53.

TABLE 53.

	Lot 1.	Lot 2.	Lot 3.
Distance from anode - -	10 cms.	10 cms.	—
Spark gap - - - -	6 ,,	17 ,,	Controls
Rays absorbed by tumour	50 per cent.	10 per cent.	—
Result of inoculation of 15 mice - - - -	0 positive 15 negative	10 positive 5 negative	14 positive 1 negative

The authors conclude from these and similar observations that the action of the rays is rather to hinder the subsequent growth of the tumours than to prevent their "taking" on inoculation, for though the percentage of successful inoculations may not be much reduced, the rate of growth of the tumours is much lessened. This is quite analogous to the effect of radium emanation upon the cells of Jensen's rat sarcoma, already referred to.

In many cases, where the histological features of the irradiated tumours were under investigation, only a small portion of the growth was exposed to the rays, the remainder being protected by a stout lead screen. In one tumour examined by Contamin, only a small area the size of a pea, was so exposed; the remainder of the neoplasm thus serving as a convenient control. Two exposures of one hour were given on two consecutive days; four days after the first irradiation the tumour was removed and prepared for histological examination.

The non-irradiated parts of the growth presented the characters of a glandular carcinoma, the cells having comparatively little cytoplasm and the nuclei being round or oval. The general connective tissue stroma divided the growth into lobules, which in turn were subdivided again and again by smaller trabeculæ. In some situations hæmorrhages were noted and were situated either in the stroma or in the essentially cellular acini of the growth.

In the irradiated area, the most marked change was the formation of cavities resembling cysts, which originated in the centre of the cellular masses constituting the acini of the growth. Their walls were formed by the neoplastic cells themselves, which in consequence of the pressure exerted upon them by the contents of the cyst had become flattened and otherwise more or less distorted. In certain situations, the largest of these cysts had reached the periphery of the cell islet, in whose centre they had originated, and in consequence had come in contact with the connective tissue stroma. The fibrous trabeculæ of the stroma were found to have undergone a considerable amount of compression while, owing to the comparatively unyielding character of the connective tissue itself, the outline of the cyst underwent an alteration from its normal circular or oval form and became more or less irregular. The cyst contents, after treatment with the usual histological fixing agents, presented a finely granular appearance, while in the largest cysts hæmorrhages were of frequent occurrence. In addition to this cystic change, a prominent feature was the marked increase in the amount of stroma. The constituent fibres were densely packed together, and in addition, the nuclei of the connective tissue cells were elongated and abnormal in contour. A considerable diminution in the number of neoplastic cells was observed and those which survived were more or less

segregated into small groups by the greatly hypertrophied stroma. These cell groups were, however, observed not to be compact, but on the contrary, here and there were clear spaces and islands of degenerated cells. Another feature of the cell groups was that they were retracted from the stroma, so that they did not lie in contact with it, a condition in marked contrast to that obtaining in the non-irradiated areas, where the connection between the neoplastic cells and the stroma was remarkably close and intimate.

In the case of tumours removed eight days after the initial radiation, cysts were, generally speaking, absent; the main feature was the enormous increase in the stroma and the consequent subdivision of the cell masses into yet smaller islets, the sections presenting an appearance as if the cells were undergoing strangulation by the fibrous tissue.

If a mouse bearing a tumour be exposed to X rays, the tumour excised and portions of it grafted into normal mice, then, after slight irradiation, the grafts develop into tumours, but do not grow so quickly as the untreated tumour; with longer exposure, the graft may remain in the animal for weeks without showing any sign of growth and may then very slowly develop into a tumour; with still more prolonged exposure, no growth at all takes place. A tumour which has received this lethal dose shows no histological changes if it be examined at once (*i.e.* a few hours after the exposure), but if it be left in the animal and portions be removed on succeeding days, certain degenerative features begin to make their appearance, and these changes are generally quite well established by the fifth or sixth day, the time depending upon the type of tumour. These degenerative features are not incompatible with the successful transplantation of the tumour and this feature has been used to advantage by Marie, Clunet and Raulot-Lapointe, in a study upon the heredity of the characters imposed upon tumours when they are exposed to X rays. The material selected was a sarcoma of the mouse (tumour A), a rapidly-growing tumour of a high degree of malignancy, with extremely stable histological features. A mouse bearing the tumour was exposed to a strong dose (30H) of unfiltered X rays, and five days later the animal was killed and portions of the tumour grafted into a number of mice; when this irradiated graft had grown to a suitable size, one was selected and submitted to

the same dose of X rays, and five days later, portions of it were again grafted into a number of mice ; in this way the irradiated tumour was kept growing for 20 months and the new characters imposed upon it by the X rays were thoroughly established. These new characters were found to consist mainly of (1) a reduction in the percentage of successful grafts, (2) a reduction in the malignancy of the tumour, (3) a slower rate of growth and certain

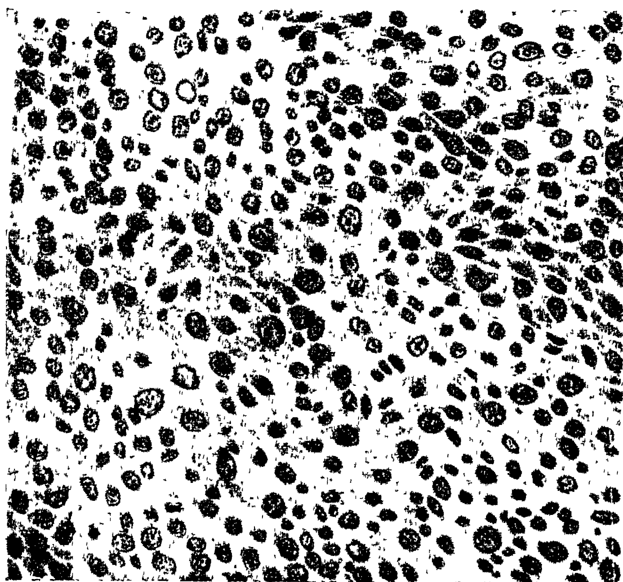


FIG. 53.

Polymorphic sarcoma of the mouse. No change in the histological features was noticeable over a period of 2½ years. Magnification 500 diameters.

histological features of which the following were the most important: (*a*) the presence of "giant" cells, some cells being as much as four or five times their original diameter, (*b*) atypical mitoses, (*c*) basophile "giant" cells, having multiple nuclei.

The question which these authors set themselves to decide was whether these new characters would be transmitted in the daughter cells, if they were entirely removed from the direct influence of the X rays. This was tested by taking one of the tumours showing these newly-acquired characters and grafting portions of it into a number of mice ; when the resulting tumours were sufficiently large, portions were again grafted ; this was

repeated through six generations, during which period there was no exposure to X rays. Histological examination of the tumour throughout this period showed a tendency on the part of the cells to return to their normal condition, but even in the sixth generation there were many cells to be seen, showing the abnormalities (*a*), (*b*), (*c*), produced in the tumour cells by their previous exposure to X rays. These newly-acquired characters,

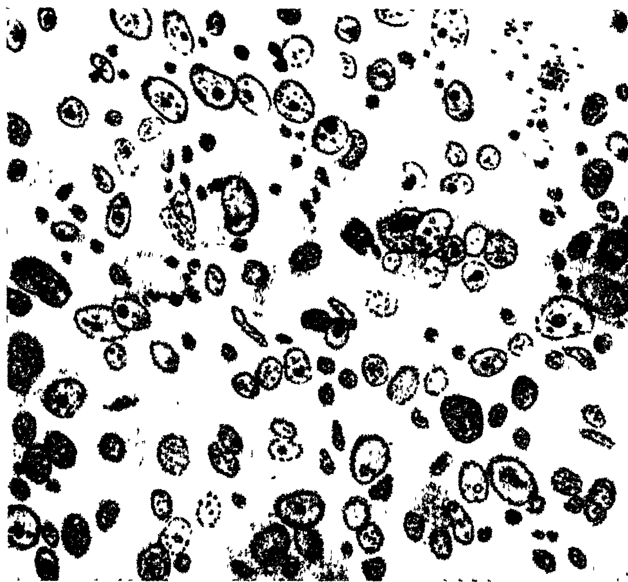


Fig. 54
Polymorphic sarcoma of the mouse five days after having been exposed to unscreened X rays (dose 30H). The chief feature to be observed is the enlargement of the cells. Magnification 500 diameters.

therefore, were transmitted to the cells in many succeeding generations. Apart from the general interest of such a result, it is clearly of great significance in many aspects of radio-therapy. If malignant cells in the human subject gradually assume less and less malignant features when exposed to X rays, this may only be manifested at some period remote from the time of exposure.

It is difficult to study the comparative effects of hard and soft X rays upon these tumours in a quantitative manner, though one can hardly doubt the desirability of determining the relative sensibility of various types of tumour to that range of the X ray

spectrum which has clinical application. Some observations were made by Wedd and Russ on a mouse carcinoma (Twort) by submitting it to measured doses of X rays after its removal from the animal. The time required for a lethal effect, *i.e.* to prevent its subsequent growth when inoculated into other mice, was found to be much shorter when the tumour cells were exposed to " soft " X rays than when only hard rays were used, the softer

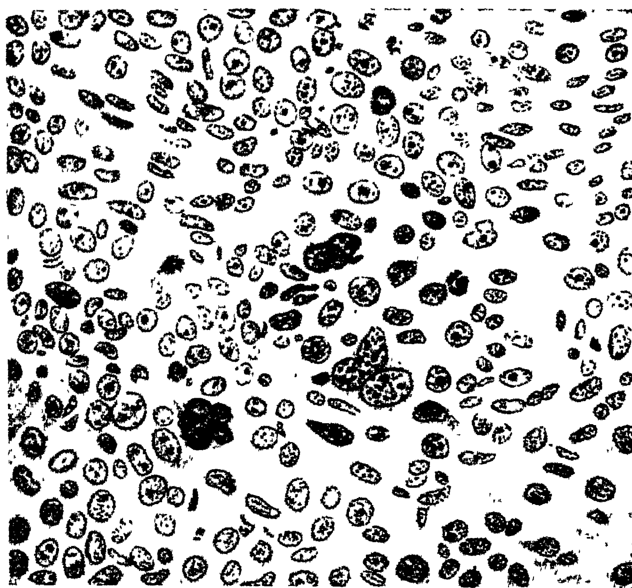


FIG. 55.

Polymorphic sarcoma of the mouse. The original tumour (Fig. 53) had been irradiated five days before grafting; this was continued over a period of two years, the new histological features (Fig. 54) being thoroughly established—the tumour was then propagated without any preceding exposure to X rays; after six generations spread over four months (Fig. 55) shows that many of the "acquired" features still persist. Magnification 500 diameters.

types being previously removed by filters. This result does not mean that the soft X rays had in any sense a specific action upon the carcinoma cells, for the result of screening an X-ray bulb, running at a spark gap of about 16 cms. by 1.12 mm. of aluminium, is to reduce the ionising power of the emergent X-ray beam to about one-third of its unscreened value (*vide* p. 23), and it is worthy of note that to obtain a lethal effect upon the tumour cells, the exposure with screened rays has to be increased about three times. This is not cited as a proof that the action of the

rays upon living cells is proportional to the ionising power of the rays; there are perhaps as many instances in which this is the case as when it is certainly not valid; these matters are considered in more detail in Chap. XX.

TABLE 54.

Conditions of Radiation.						Number of Mice.		Growth.	
	Current.		Spark-gap.	Screen	Time of Irradiation	Inoculated.	Survived.	Positive.	Negative.
	Primary.	Secondary							
	Amperes	Milliamperes.	Cm						
Series 1	4	0.8	6	None	15 minutes	5	4	1	3
	4	0 8	6	"	30 "	5	4	0	4
	4	0.6	8	"	1 hour	8	7	0	7
					Controls	13	11	10	1
Series 2	4	0.7	6–7.5	0.56 mm. Al.	30 minutes	8	4	3	1
	4	0.4	"	"	1 hour	8	5	0	5
	4	—	—	"	2½ hours	6	4	0	4
			"		*Controls*	21	13	11	2
Series 3	4	0.4	14	1.12 mm. Al.	1 hour	8	5	2	3
	4	0.4	14	"	1½ hours	8	8	6	2
	4	0.35	16	"	2 "	7	6	0	6
					Controls	23	16	9	7

Some of the most extensive and elaborate researches into the nature of the changes produced in malignant cells when subjected to X rays have been made by Clunet and Raulot-Lapointe, the details of which may be found in Clunet's *Tumeurs Malignes* (1910). We shall here confine our attention to the broad general features of these researches, which include carcinomata and sarcomata.

The procedure adopted by these authors has been to treat the malignant condition with X rays, and at various stages of the treatment to obtain portions of the growth for histological study.

As a result of observations of this nature upon nineteen cases of squamous cell carcinoma of Malpighian type in the human subject, they state that before the ultimate disappearance of the growth, the cells pass through at least five successive phases which are characterised as follows:

(1) The latent phase.

(2) Development of monstrous characters.

(3) Keratinisation.
(4) Disintegration and phagocytosis.
(5) Formation of the connective tissue scar.

(1) *The latent phase* varies from 6–15 days and during this time no cytological changes are to be seen. Its duration is rather shorter for carcinomata of the spino-cellular type than for the baso-cellular.

(2) *The development of monstrous characters* is marked by :—

(*a*) An enlargement of all parts of the cells, which may be increased in diameter as much as two or three times.

(*b*) An increased number of atypical mitoses.

(*c*) The appearance of enlarged nuclei, markedly chromophile.

(*d*) The appearance within the cells of forms having a pseudo-parasitic character.

(3) *Keratinisation* may be either disseminated, total or atypical. When disseminated, each cell undergoes keratinisation independently of its neighbour, in contrast to those effects appearing to influence all cells alike. When atypical keratinisation is observed, the protoplasm becomes granular, at first orangeophile and finally eosinophile ; these granules gradually fuse together into one mass of keratin, and although they are probably similar in their chemical constitution to eleidin, they do not give the same colour reactions as this substance.

The nucleus is subject to an evolution which varies with the particular case ; sometimes there is karyorrhexis, then diffusion into the protoplasm ; sometimes the nucleus becomes clear and acidophile granulations appear in it and a transformation into a mass of keratin follows. Nuclear keratinisation may, however, occur without the pycnotic stage ; the process then appears to begin in the nucleolus, and in some cells this seems to precede the transformation occurring in the other parts of the cells.

(4) *Disintegration and phagocytosis.* The disintegration of the degenerating cells appears to be caused mainly by the polynuclear cells and the fibroblasts of the stroma, which are in an active condition. Macrophages and plasma cells appear at a later stage and accumulate around the vessels, remaining in the vicinity long after the disappearance of the malignant cells. At the periphery of the keratinised masses plasmodia are sometimes found, simulating the type presented by the cells of the neoplasm, but they are rarely found in great numbers. The masses

of degenerate cells, before becoming entirely destroyed, may cease to give the colour reactions of keratin, and remain encapsuled in the dermis for prolonged periods.

(5) *Formation of the connective tissue scar.* As a general rule this is not brought about by the formation of fibrous masses, but the tissues assume the structure of healthy skin, except for the absence of hair and of glands; the elastic fibres are also less numerous and more attenuated than they are normally. No neoplastic masses are to be found in these supple scars, which appear to be quite healthy; on the other hand, at a depth below the skin, cells may be found which have been acted upon by the X rays, but are not yet destroyed; such cells remain in a latent condition, and if the treatment is not continued, they give rise to recurrences. They are distinguished by a very chromophilic nucleus, though not pycnotic, a reduced amount of protoplasm and an avidity for basic colouring material.

Apart from their cytological interest, these five phases serve as a most useful guide in estimating the stage that the cells of a neoplasm have reached in the evolution which terminates in their extinction.

As illustrating in a clear manner the most evident phases assumed by carcinoma cells when exposed to X rays, four figures (Pl. I.) are reproduced of a superficial carcinoma of the cheek, described by Clunet in the following manner: "The tumour histologically was an atypical epithelioma of the skin, in which there were no spinous connections between the cells and very little horny degeneration." The biopsy made before any X-ray application showed a condition indicated by Fig. 56; ten days after exposure to X rays, the cells showed enlargement and increased karyokinetic changes (Fig. 57). A specimen of the growth obtained three weeks after treatment reveals the degenerative condition considerably advanced (Fig. 58), and a section taken after the tumour had apparently disappeared, illustrated in Fig. 59, shows a region almost entirely made up of young connective tissue cells. A careful inspection, however, led Clunet to the following findings: "Looking more closely, however, I found some cells with many nuclei, and the conclusion is forced upon one that these are perhaps giant cells, the last remains of the battle which has been fought out in the tissues. There are also some dark cuboidal cells, of epithelial nature, which have not

been killed by X rays, but have remained in a kind of lethargic condition. Their presence in similar cases may explain why it is that patients macroscopically cured subsequently show a recurrence of the tumour. I think the results of this biopsy are very important from the point of view of recurrence after X-ray treatment."

Their studies upon mammary carcinoma led to almost identical findings as to the manner in which, after a sufficient amount of irradiation, the malignant cells disappear. A case of multiple cutaneous metastases in the breast was made the subject of detailed study by Menetrier and Clunet, a description of which may be found in *Archives de Médecine Expérimentale*, p. 159, 1908. Certain of the cutaneous nodules were selected for treatment and comparison made between them and adjacent nodules, which had received no rays ; the effect of the radiation diminished in intensity as the depth below the surface increased, and this allowed every phase and character of the changes induced in the irradiated cells to be studied ; it is sufficient for our present purposes to point out the essentially gradual nature of the changes consequent upon irradiation ; there is no immediate destruction such as occurs with caustic agents, or as the result of exposure to high temperatures.

When sarcomatous growths are exposed to X rays, Clunet and Raulot-Lapointe found that a somewhat similar transition in the cellular characteristics occurs, but the latent phase, during which no changes are observable, is very much shorter than in the other types of malignant growth considered ; instead of being from 6–10 days, it is generally 1 or 2 days.

A spindle-cell sarcoma studied by these authors showed a particularly interesting evolution after receiving a rather small quantity of unfiltered X rays (9H). We quote from their description, which is as follows : " The fibro-sarcomatous zone separating the granulation tissue from the normal dermis on one side, and from the pure sarcoma on the other, seems to show that at a certain depth, the rays, although too feeble to destroy the neoplastic cells of the connective tissue, have nevertheless caused a profound alteration in the biological evolution of these cells ; the rays have caused the cells to secrete collagen and to take on the morphological characters of a fibroma, a benign tumour."

These findings are especially interesting in their general resemblance to those of Dominici upon a fibro-sarcoma exposed to the gamma rays of radium (p. 291). When a conclusion of this kind is reached independently by various observers, the probability that the interpretation has been a correct one is greatly increased.

Without building too much upon the facts, it is not without interest to consider the significance of the foregoing observations from the point of view of cellular reaction. If, as a result of exposure to X rays, certain sarcoma cells are transformed into fibroblasts, the exact conditions of irradiation necessary to bring this about are of the utmost importance. The possibility may reasonably present itself to us that such a process is a reversible one; if the experimental production of sarcoma in the rat by exposure to X rays (p. 317) has been brought about by some change in the normal evolution of the connective tissue, the possibility becomes a probability. If such, indeed, be the mechanism by which these sarcomatous growths originated, it is to be observed that, whereas the change in evolution of the sarcoma cells into fibroblasts was brought about by a comparatively small dose of X rays, a very large amount of X-ray energy was apparently required to cause the change of the normal connective tissue cells to those of a malignant character.

It has been established that not only do different types of malignant growth react in varying manner and degree when exposed to X rays, but the same tumour may exhibit a different degree of sensitiveness to the rays when these are applied at various intervals of time.

Nogier and Regaud have submitted evidence, based upon a clinical experience of over one hundred cases of malignant growths, that there often occurs a gradual diminution in the sensitiveness of these growths to X rays; the clinical indication is that when a growth is exposed for the first time to X rays a marked diminution in its size may occur, but when the rays are again applied after an interval of some days or weeks, the same dose of X rays does not now appear to be so effective, and succeeding applications of the rays may have no apparent effect upon the growth. The remaining cells of the neoplasm appear to have become more resistant to the rays. This observation is of considerable importance from a radio-therapeutic point of view, for it should decide

to some extent the method by which radiation is best administered to growths which exhibit this phenomenon.

Seitz and Wintz have within recent years attempted to express the dose of X rays required to cause the disappearance of various types of human tumours in terms of the skin dose. In most cases they find that the lethal dose for the tumour is greater than that which provokes a marked reaction in the skin. Considerable use is made of these data by Wintz and others in the therapeutic uses of X rays. It may prove to be of much value in estimating the dose of radiation given to a tumour to be able to refer this to a quantity which has a definite action upon the skin. This is but one aspect of the difficult subject of dosage in radio-therapy and it seems likely that measurements will remain on a basis of comparison until some definite unit of X-ray energy is established.

There is little doubt that the various types of malignant growth in man exhibit a wide range of susceptibility to the rays from radium and X rays, and it is very improbable that the widely different clinical results recorded in radio-therapy are to be attributed solely to differences in technique. To what extent the histological type of growth, rapidity of growth, mode of extension, vascular supply and resisting power of adjacent normal tissues contribute to these observed differences in mode of reaction, is, of course, a question the answer to which can only be given when further evidence upon each aspect of the subject is forthcoming. It is rather a striking fact that when the lethal dose is determined, by the method described on p. 282, for animal tumours of completely different histological type, very small differences in this dose are found.

Thus Wood and Prime found that only small differences were detectable in the dose of radiation necessary to prevent growth of the following varieties of animal tumours, viz., Flexner Jobling rat carcinoma, Ehrlich spindle-cell mouse sarcoma, and No. 11 and No. 180 Crocker mouse carcinoma. Again, for two rat sarcomas (one of very rapid the other of very slow growth), and for a rat carcinoma the lethal doses were found by Russ, Chambers and Scott to vary no more than about 10 per cent. for the three varieties. In so far as observations upon animal tumours have any application in the radiological treatment of malignant disease, the results first cited tend to direct attention

to the part played by the resistance of the animal; for it seems highly unlikely that the wide differences, both in degree and nature of reaction, exhibited clinically by malignant growths when exposed to radiation can be referred simply to differences in their histological type. It seems more probable that the relationship which such tumours bear to the normal tissues of the host, their blood supply, their rate of growth, and possibly other factors, will all play some part in determining the subsequent fate of the malignant cells after the radiation has been administered to them.

We may remark here that when X rays or the rays from radium are applied to the surface of the body, with a view to the treatment of a malignant tumour at some depth below the surface, one of the most important considerations, perhaps indeed the dominant consideration for the radiologist, is what dose of radiation the skin will tolerate. In many cases he knows that the dose that he would like to administer to the tumour cells is too great for the skin to bear without suffering some damage; in order, however, to administer the requisite dose he may adopt various ports of entry, and to a certain extent the probability of causing damage to the skin is diminished. Under other conditions of radiotherapy, for example when radium enclosed in small platinum tubes is inserted into a malignant growth, the skin reaction is not relevant, but it is no less important for the radiologist to have some knowledge as to the nature and extent of the reactions of the various normal tissues which may be contiguous to the actively proliferating malignant growth which he is endeavouring to arrest.

Animals given a large generalised dose of X rays or the gamma rays of radium are so affected thereby that they die in the course of a few days. It is an experimental matter to decide whether with a reduction in such exposures any changes of a constitutional character are observed. The effect of very small repeated doses of X rays upon rats has been investigated by Russ, Chambers and Scott, who submitted batches of these animals to daily doses of moderately penetrating X rays for different periods of time. Observations were made upon the changes in body weight of the animals and upon the resistance which they offered to inoculations of a sarcoma. Comparison was made in these two respects with batches of non-irradiated animals, kept as controls.

The data in Table (X) show that when rats are given generalised X-ray exposures daily for some weeks before being inoculated the animals appear to have an additional resistance towards the growth of tumour inoculated into them.

TABLE (X)

Period of irradiation	Interval before inoculation.	Number of animals	Volume of tumour compared with that of controls. Time after inoculation			Remarks on tumour growth
			2 weeks.	3 weeks	4 weeks	
4 weeks	28 days	18 X-rayed 26 controls	0.77	0.46	0.40	X-rayed animals grew 4 progressive tumours 14 disappearing tumours Control animals grew 12 progressive tumours. 14 disappearing tumours
6 weeks	13 days	9 X-rayed 10 controls	0.65	0.44	—	X-rayed-animals grew 3 progressive tumours. 6 disappearing tumours Control animals grew 9 progressive tumours. 1 disappearing tumour
8 weeks	11 days	21 X-rayed 20 controls	0.42	0.40	0.35	X-rayed animals grew 7 progressive tumours. 14 disappearing tumours. Control animals grew 14 progressive tumours. 6 disappearing tumours.
12 weeks	13 days	29 X-rayed 24 controls	0.84	0.76	0.65	X-rayed animals grew 19 progressive tumours. 10 disappearing tumours. Control animals grew 17 progressive tumours. 7 disappearing tumours
X-ray exposures for 12 seconds daily.						

The effects of different doses upon the normal growth of the animal are shown in Table (Y), from which it appears that the same dose which tends to increase the animal's resistance towards the tumour results in a slightly increased rate of growth of the

animal, comparison in each case being made with the normal mode of the non-irradiated animal.

TABLE (Y).

Number of X-rayed animals	Exposure to X rays	Effect upon body weight
16	1 minute daily for 9 weeks	*Result*: 25 per cent. diminution below normal rate of growth in 63 days. (All but 4 died)
22	12 seconds daily for 8 weeks	*Result*: 15 per cent. increase above normal rate of growth in 62 days
21	12 seconds daily for 4 weeks	*Result*: 7.5 per cent. increase above normal rate of growth in 50 days.
23	2 seconds daily for 9 weeks	*Result*: 10 per cent. increase above normal rate of growth in 69 days.

Murphy and Morton have recorded the results of an attempt to increase the resistance of mice towards their own spontaneous tumours. Particular interest centres round such an attempt, for it is generally held that an animal has very little resistance to a spontaneous tumour occurring in it; there is, however, great difficulty in the successful transplantation of these spontaneous tumours into the normal species. The experiment of these authors was to collect a number of mice suffering from spontaneous tumours, these were removed as completely as possible by operation, the whole animal was then subjected to a generalised dose of X rays, and immediately afterwards a graft of the original tumour was inoculated into the groin. In twenty-six out of fifty-two mice treated in this way the grafts did not produce tumours, nor were there recurrences at the site of operation; in the remaining half the grafts grew and in all of the mice recurrences occurred. As controls twenty-nine mice with spontaneous tumours of various sorts were selected. An identical procedure, but without X rays, resulted in twenty-eight of the grafts growing into tumours, local recurrence at the site of operation occurring

in fourteen cases. The authors were not at the time of these experiments able to specify the quantity of X rays used, nor, indeed, do they state the nature of the spontaneous tumours under test; it is probable that for these reasons there have, to our knowledge, been no attempts at confirming what is a very striking result.

Animals may be made immune, by a variety of means, towards inoculations of tumours, and the literature of this subject is an extensive one. It has been shown by Ehrlich and by Bashford, Murray and Russell among others that, by the inoculation of an animal with spleen or embryonic tissue or even blood cells, a certain degree of immunity towards subsequent tumour inoculations results; the degree depends both upon the amount of material inoculated and the interval elapsing between this and the test inoculation. Generally speaking, this immunity is not of a permanent character, and in this respect it resembles the immunity towards bacterial infections by vaccines. For details of the various ways of rendering animals resistant to tumour transplantations the reader is referred to the reports of the Imperial Cancer Research Fund.

We have seen on p. 285 that when a tumour is removed from a mouse, given the dose of radiation lethal to it, and small portions of it inoculated into normally susceptible mice they do not grow to form tumours; they are absorbed and no trace of them can be found from ten to seven days later. In many cases the animals are found to be immune to a re-inoculation of the normal non-irradiated tumour; the feature of this immunity is that it is of practically a permanent character; rats which have been made immune to Jensen's rat sarcoma by this means have been kept for over a year and found by subsequent inoculation to be still resistant to the tumour in question.

Murphy and Taylor showed that if immune mice were given a comparatively large generalised dose of X rays and subsequently inoculated with a fragment of the tumour (adeno-carcinoma) to which they were previously immune, tumours now formed in the animals; the extent to which this took place may be seen from the chart in Fig. (60).

A similar action was shown by Mottram and Russ in the case of rats which were immune to Jensen's rat sarcoma, a tumour to which they are ordinarily very susceptible.

In both of these cases the radiation to which the animals were exposed were large doses, and such findings may have some

IMMUNIZED IMMUNIZED+X-RAYED CONTROLS

Weeks after Test Inoculation

1 2 1 2 1 2

FIG (60).—The silhouettes represent the tumours in the three different series of mice.

bearing upon the administration of large doses of radiation in the treatment of malignant disease in man. It is admittedly an

urgent matter, and one demanding many technical considerations to deliver to malignant cells in the body a dose of radiation which shall be lethal to these cells, but it may be well worthy of consideration to what extent such radiation may be decreasing the normal resistance of the host. If safe means can be found whereby this resistance is actually increased, it may be profitable to employ it simultaneously with the main radiation directed upon the actively growing and invading malignant cells.

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CHAPTER XVII

THE PRODUCTION OF MALIGNANT DISEASE

ON THE PRODUCTION OF MALIGNANT GROWTHS BY THE RAYS.

It is a melancholy fact that X rays, when applied for prolonged periods to the human body, may set up a condition of malignancy in the parts irradiated. The earliest radiologists have suffered especially in this manner, subjected as they were in the earlier years to fractional doses of the rays they were administering, and it is an observation worthy of record that the lesions have most frequently appeared on the left hand of the operator, this being more exposed than the right hand during screen examinations; moreover, the primary lesions rarely extended beyond the line of the cuff or sleeve. This is significant, in showing the special danger of exposure to soft X rays, for these rays alone would be cut out to any appreciable extent by the thickness of an ordinary coat sleeve.

The significant fact, therefore, is that repeated small doses of soft X rays, when applied to the human tissues, produce gradual changes therein, which may cause such tissues to develop malignant features. The transformation of the normal cells into some malignant form is, under these circumstances, a very gradual process, and examination of the surface of a typical case of radio-dermatitis reveals the existence of parts showing hypertrophy as well as atrophy. That the rays are capable of bringing about both of these changes seems to be proved; but whether for the next stage, namely, the appearance of the malignant cells, any additional factor such as an external parasite is necessary, cannot be said to be proved in either sense. It has been argued that tissues whose resistance is lowered by prolonged irradiation are

more likely to be adversely affected by the supposed agents of malignancy than the undamaged normal tissues; on the other hand, there is no difficulty in supposing that the rays are of themselves capable of producing exactly those changes (chemical or physical) which the hypothetical causes of cancer are thought to bring about.

We have seen that many animals, when exposed to the rays, respond in a similar way to man in many particulars. An investigation has been made by Marie, Clunet and Raulot-Lapointe, the object of which was the production of a malignant growth in an animal by subjecting it to prolonged radiation by X rays. They exposed a number of white rats to massive doses of X rays, as a result of which a severe radio-dermatitis ensued. The animals were allowed to recover from this and were then given a further exposure to X rays, the radio-dermatitis and cicatrisation occurring in some cases three or four times. In two cases they have observed the formation of a sarcoma in the region of the radio-dermatitis. The evidence for the growth being a true sarcoma is discussed very fully by these authors; from the histological point of view, the tumours were indistinguishable from a pure spindle cell sarcoma, the structure being perfectly homogeneous; from the standpoint of malignancy, the neoplastic tissue recurred after operation; it grew in muscle and peritoneum and destroyed those normal tissues, without any inflammatory reactions.

One of the observations of these authors is of particular interest; they noticed that after the first dermatitis had healed, the dose of X rays necessary to reproduce the condition was much less than initially, indicating that the cells had become more sensitive to the rays. This has a direct clinical parallel, for a skin surface which has suffered from exposure to X rays is found to be more susceptible to their action on subsequent exposure.

A further attempt at the production of a malignant growth in animals by means of radiation was made by Lazarus-Barlow; the experiments were made upon rats and rabbits. The rats, fifty-three in number, were inoculated subcutaneously with small glass tubes, containing quantities of radium which varied between 0.001 and 0.15 milligram of radium; with the stronger radiation the microscopic findings were loss of hair and formation of ulcers; microscopic examination showed a down growth of the epidermis

and the formation of cell nests. In only one case did the epithelial down-growth invade the subjacent muscular layer.

The experimental arrangements were different in the case of the rabbits; here a small quantity of radium was inserted and sealed into the middle of a gall-stone, which was then put into the gall bladder of the animal. They lived for periods ranging from one to four years, when microscopical examinations were made. The most striking feature observed was an irregular proliferation of the columnar cells, simulating in some respects a columnar cell carcinoma. As the result of a number of observations the author remarks that it is a comparatively easy matter to reach stages which would be deemed precursors of the cancerous condition, but that some other factors seem necessary for the actual production of a tumour in the animals.

The first detailed histological description of a malignant growth in man caused by X rays was given in 1906 by de Beurmann, Dominici and Gougerot. The case was that of a radiologist whose hand had suffered from too great exposure during a period of four years. The first phase, one of dermatitis, was characterised by tumefactions, hypertrophy of the cutaneous folds and by desquamation. This phase was followed by more serious lesions; the skin became thinned, shiny and atrophic, while the cutaneous appendages (hairs, sweat and sebaceous glands) disappeared The general conditions showed a state of erythema, of capillary dilatation and of local pigmentation, while here and there epidermal proliferation manifested itself in the form of plaques of epithelial cells. In addition to these lesions the troubles were accentuated by the occurrence of ulcers, due in part simply to bacterial invasion, but also to the obliteration of small blood-vessels; this latter was a result of the damage to the endothelium of the blood-vessels, consequent upon their exposure to the rays.

Such ulcers are very slow in healing and may be the site subsequently of squamous cell carcinomata; clinically and histologically they resemble ordinary squamous cell carcinoma of the skin, but they have a tendency to remain localised; so much so that an early and free removal of the growth affords a reasonable hope of there being no subsequent recurrence.

The growth in question was found to be a typical epithelioma; there were no metastases, although the lymphatic capillaries were invaded by malignant cells.

Clunet, in 1910, described in detail a case bearing in many respects a striking similarity to that above. A tumour appeared at the extremity of the finger of a radiologist who had suffered from repeated exposure for a number of years; the finger had been in a chronically ulcerated condition for some years before the appearance of the malignant growth. The main features, which may be clearly seen in Fig. 60, are the three zones which are characterised by different degrees of cellular change produced by the rays; the zone exhibiting papillomatous hyperplasia is separated from that in which malignant cells are present by an intermediate transition zone. It is difficult to determine the particular stage in this transition zone which marks the onset of malignancy.



Fig. 61 —*E*, interpapillary hypertrophy. *G*, region where the neoplasm starts, commencement of atypical cells, this is also the limit of the ulceration.

Clunet's *Tumeurs Malignes*, p. 290

Clunet states that a few millimetres further on in the section than is here depicted the malignant cells may be seen to invade and destroy the subcutaneous tissue.

The two cases of Röntgen ray carcinoma which have been considered in some detail may be considered as typical examples of the result of chronic exposure to X rays in man. Reviewing the data available on the subject in 1911, Krause states that at that time there was undoubted proof of malignant disease having been set up in this manner in 54 cases, which were distributed in the following manner:

France	2	Germany	13
England	13	America	26

Of these, 26 cases occurred among practising radiologists or their assistants, 24 among those engaged in technical work

upon X rays and 4 were among patients. The most frequent site of the malignant growth was the back of the hand and the fingers; such growths were always associated with some pathological condition of the skin; in 50 of the cases dermatitis was present, frequently to the extent of an ulcerated condition. Krause states that the most frequent type of growth induced by the X-ray exposures is carcinoma; in only one case was a sarcomatous growth found, and this was a sequel to the irradiation of a lupus. Apart from the occurrence of these malignant growths, there appears to be a number of cases in which the irradiation of a lupus has resulted in the subsequent appearance of a carcinoma; according to Krause there were, up to 1911, 27 such cases recorded.

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CHAPTER XVIII

IDIOSYNCRASY AND DOSAGE.

IT is a matter of no little difficulty to decide the extent of idiosyncrasy in the human subject to X rays. Slight variations in technique might of themselves account for the supposed idiosyncrasy and, with a view to obtaining a general opinion on the subject, Arcelin addressed the following enquiries to radiologists, with the following results :—

(1) Do cases of idiosyncrasy exist; that is to say, is an untoward reaction apt to occur as the result of exposing the human skin to a normal dose of X rays, equal to or less than that which, in the majority of cases produces only an erythema? (Normal dose, tint B, Sabouraud et Noiré; tint 1, Bordier; 625 M, Guilleminot.) Seven radiologists of repute were of opinion that real idiosyncrasies exist. Six radiologists of repute had not seen real idiosyncrasies, and were of the opinion that apparent cases were due to errors in measurement of the dose administered.

(2) What interval of time should be given between the first dose and the second, between the second and third, and so on, to avoid harmful reaction of the skin? The replies showed no approach to agreement as to whether it is better to give always the same dose, to give small doses repeatedly, or large doses seldom, in order to avoid reaction.

(3) If the skin has received several doses of X rays without damage, does it become sensitised? If the skin receive a normal dose some time after (months or years), is it likely to be seriously damaged? When the initial treatment has been of short duration, the skin may receive the same dose without harm six months later. When, however, the treatment has lasted a long time, the skin becomes atrophied and a small dose of X rays may be dangerous.

(4) If the skin be treated without accident, can it give rise to trophic lesions several years after all treatment is stopped? When the exposure has been of short duration and without evident reaction on the part of the skin, this is not likely to occur, except in certain unhealthy skins, *e.g.* eczematous. When, however, the skin has suffered an initial reaction, subsequent disturbances are very easily induced.

(5) If the skin be exposed to radiation, may it give rise to disturbances in the skin of a neighbouring region? M. Nogier cites seven cases in which this has occurred.

There is little reason to doubt that an idiosyncrasy actually exists in the sense that the same dose of radiation will provoke a reaction, the degree of which varies with the individual; moreover, the same person may react at different times to a varying degree when exposed to the same dose of rays, and in this connection Knox has drawn attention to the part played by the circulation; a surface whose blood supply is temporarily impoverished is observed to react to a much smaller degree than when measures are taken to induce a liberal flow of blood to the part; it seems not unreasonable to associate such an effect with the secondary radiation, which would undoubtedly be emitted by the iron in the circulating blood.

Apart from the question of idiosyncrasy, however, there must come a stage at which the equivalence of a large dose acting for a short time and a small dose acting for a long time, must be lost. This is not only the case for X rays, but is an important consideration in radium-therapy. Pearce Gould has uttered a timely warning against the use of such terms as "milli-gram hours"; such an expression as "100 milli-gram hours" would apparently equally describe the application of 100 milligrams for one hour, or of 1 milligram acting for 100 hours; it is quite certain that in many cases the two different procedures would provoke reactions little in common. The "dosage" is a complex quantity and includes the quantity of radio-active material, the volume in which it is contained or the area over which it is spread, the nature of the rays selected and the time for which they are applied.

Lazarus-Barlow has made a study of the way in which various types of cells react to the same dose of rays (radium); this dose in two comparative series of experiments being made up of (1) a

large quantity $Q = 92$ milligrams of radium bromide, acting for a short time $t = 13\frac{1}{2}$ minutes, and (2) a small quantity $q = 38$ milligrams, acting for a correspondingly longer time $T = 30$ minutes. It was found that the 92 milligrams, acting for 13½ minutes, caused the same amount of ionisation as the 38 milligrams, acting for 30 minutes; the thickness of the platinum tube holding the radium was not quite the same in the two cases.

The experiments were conducted in the following manner: the platinum tube containing the radium was placed in the rectum of a rat for a certain length of time, when it was removed and examination made of the various cells which had been exposed to the radiation.

The region selected was the lower end of the rectum, together with the adjoining portion of the under-surface of the tail; in this way the effect of the same dose of rays upon three different varieties of epithelial cells, viz. dry squamous, moist squamous and columnar, was determined.

An animal of each series was killed on the 1st, 2nd, 3rd, 7th, 8th and 9th days after exposure to radium; the irradiated portion of the rectum and under-surface of the tail were removed, so that a single section could be prepared of the whole region to be examined. Considerable differences were found in the reaction of the various types of cells, the main features being as follows:

Columnar region. During the period 1–3 days after exposure, 92 mgs. acting for 13½ minutes (dose 1) produces more interference with mitosis and less inflammatory reaction at the site of contact with the radium tube than was produced by 38 milligrams acting for 30 minutes (dose 2); but less stimulation of mitosis and inflammatory reaction occurred at a short distance from the tube. As regards general degenerative changes, such as mucoid degeneration, formation of mucus, desquamation and alteration of nuclei, these were more marked with dose 1 than with dose 2.

During the period 7–9 days after exposure, the more profound changes are still associated with dose 1 rather than with dose 2.

Moist squamous region. In this region dose 2 produces more alteration in the cells than does dose 1. The nuclei of the cells become swollen, clear and stain badly, with reduction in the number of mitoses. The sphincter ani muscle, which lies in

close relation to the moist squamous epithelium, is also more affected by this method of applying the dose. No inflammatory changes were recognisable in this region.

Dry squamous region. In this region dose 2 produces more marked effects than does dose 1. Mitosis is hindered, the cells stain badly, and there is desquamation of the superficial keratinised layers of cells.

The observations showed that the dry squamous region was throughout more vulnerable than the moist variety.

The above example indicates perhaps the simplest way in



Fig. 62.

which the dosage may be varied, keeping the ionisation as measured by an electroscope the same throughout. Another case has been considered by Lazarus-Barlow, namely, keeping the quantity of radium constant, but screening the radiation by increasing thicknesses of platinum; inasmuch as this cuts down the ionisation, the time of exposure was lengthened so as to make the total ionisation the same in each of the cases dealt with, which were as follows :—

(*a*)	92 milligrams of	radium bromide	screened by	.5 mm.	platinum.
(*b*)	,,	,,	,,	1.0	,,
(*c*)	,,	,,	,,	1.5	,,
(*d*)	,,	,,	,,	2.0	,,

Owing to the superposition of screens of varying thickness, the tube was always made to the same diameter (8 mms.) by coating

it or the screen with the requisite thickness of paraffin wax. The procedure was to insert the tube into the lower end of the rectum of a rat, one-half of the tube lying within the gut, and the other half in contact with the skin of the root of the tail.

The rats were killed at various intervals and the irradiated regions examined in order to compare the extent of damage suffered by the tissues, the same dose being administered, but the character of the radiation varying ; with .5 mm. of platinum there is a considerable amount of hard beta and soft gamma radiation accompanying the hard gamma rays ; this becomes less and less as thicker platinum is used until, with 2 mms. of platinum, the radiation is practically hard gamma rays only.

The general result of this investigation was to show that the condition of the epithelium and sub-epithelial tissues departs from the normal to a greater extent with slight platinum screening than with heavy screening. This was the case in the columnar epithelium region at a distance from the radium tube or the columnar, moist squamous or dry squamous region in direct contact with the radium tube.

In Fig. 62 are shown low-power magnifications of preparations from the lower end of the rectum and adjacent part of the rat's tail (in the figure the mucous surfaces face one another). The upper specimen was exposed to 92 mgs. of radium bromide for 108 minutes, the lower to 38 mgs. for 240 minutes. The radium doses were therefore identical in respect of the amount of ionisation they produced. The two rats which were made the subject of the experiment were killed on the ninth day after exposure. The changes produced in the two cases differ markedly. In the upper specimen (irradiated with 92 mgs. for 108 minutes) the mucous membrane persists, while in the lower specimen (38 mgs. for 240 minutes) the inflammatory changes have been so intense that the mucous membrane in contact with the radium tube, and a little beyond it, has completely sloughed away. High magnifications show the remnants of the submucous tissue crammed with inflammatory cells, mostly polymorphonuclears. In the mucous and submucous regions the smaller quantity of radium acting for the longer time has produced the most destruction ; in the cutaneous and subcutaneous regions, however, exactly the reverse has happened, for the inflammatory reaction and destruction of

squamous cells are more marked in the rat irradiated with 92 mgs. for 108 minutes. Undesirable damage, therefore, is best eliminated by keeping the quantity factor of the radium dose high and the time factor low, in the case of the columnar cell complex; but in the case of the squamous cell complex the quantity factor should be kept low and the time factor high.

Pinch has referred to the different effects which the same dose of radiation has upon different types of malignant disease. As a result of the radium treatment of a large number of cases of malignant disease, Pinch concludes that in hypoblastic growths the optimum action results if the quantity of radiation is large and the time factor short, in epiblastic growths the reverse conditions should be arranged, whereas in treating mesoblastic growths Pinch advocates that a middle course should be adopted, *i.e.* the quantity should not be very large nor the time of exposure very prolonged.

The need for exact specification in the case of X rays is no less urgent than with radium. When it is borne in mind that clinical and general experimental use is made of X rays ranging over several octaves, the necessity for specifying the region selected is clear. The terms soft, medium and hard have served to distinguish in a comparatively rough manner various types of radiation, but with the added exactness which the determination of wave-length of X rays has conferred, it is likely and desirable enough that such terms will either be specified quite accurately as extending over certain regions of the spectrum, or be replaced by the numerical values of the wave-lengths of any radiation in question.

This is but one aspect of X-ray dosage, and a large amount of clinical and other experimental evidence has accumulated to show that no simple quantitative relation exists between the reaction of a living cell, or system of cells forming a complex organism, and the amount of radiation incident upon it; hence, wherever possible, all the factors concerned in the administration of the rays might with advantage be specified.

It should be borne in mind when speaking of a dose of X rays that we are not yet in a position to state what is the actual dose or quantity of radiation administered under experimental or clinical conditions, for no absolute unit of X ray energy has yet been decided upon, and until this is done reference to dosage

has to be made in terms of the intensity of the rays and the time for which they act; in their passage through the tissues there will be a fall in this intensity due to the increase in distance from the source of rays and to the absorption and scattering which the rays suffer. Generally speaking it would appear that a knowledge of the total dose of radiation absorbed by a tumour is not of more immediate importance than the variation of intensity of the radiation through its mass, and it will readily be seen that to obtain uniformity of this intensity through a tumour of appreciable size is a matter of great technical difficulty. In the case of exposures to radium similar considerations apply to some extent, but it is possible in some cases to specify the dose because the amount of energy given out in the form of beta and of gamma rays from a given quantity of radium is known. Hence, if we are dealing with a radium preparation emitting a beam of rays of known composition it is possible to express the reaction observed in tissues as that due to the absorption of a certain amount of energy in the form of radiation of a definite character.

We may observe here that the reaction exhibited by tissues to rays from various parts of the spectrum bears no simple relation to the amount of energy absorbed. The energy-equivalent of a beam of X rays of considerable intensity is much smaller than the marked effects upon tissues to which it gives rise would lead us to expect.

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CHAPTER XIX

PHYSIOLOGICAL

SOME PHYSIOLOGICAL ACTIONS OF THE RAYS.

In the preceding sections of this book attention has been directed to the action of radium and X rays upon certain lower forms of life, upon development and upon structural changes dependent upon their action on the tissues. In the present chapter the subject of consideration is the alteration of function due to irradiation; and here the information is much more scanty, for just as a fairly accurate knowledge of normal anatomy preceded even an approximation to the attainment of physiological truths, so in the present instance information regarding morphological changes is much more advanced than that regarding alterations in function as a sequel to irradiation.

Certain aspects of the subject are as yet highly controversial, and at present it is only possible to deal with the subject in a fragmentary manner.

For purposes of convenience, the contents of this chapter are divided into notes upon the physiological actions of

(1) Radium,
(2) Radium emanation,
(3) X rays.

The physiological effects of radium upon the eye. When a salt of radium, suitably enclosed in a capsule, is brought near to the eye in the dark, a sensation of diffuse, uniform, steady light is produced. This occurs when an opaque screen such as black paper intervenes between the radium preparation and the eye, so that the sensation of light is not due to the faint fluorescence of the radium itself. Hardy and Anderson have shown that the

effects are due to the beta and gamma rays emitted by the radium, by the following series of experiments, in which they employed 50 mgs. of radium bromide, spread out over a circle of about 5 mms. in diameter, so as to form a layer about 1 mm. in depth. On approximating this preparation, suitably covered with a black card, to the eye, the diffuse sensation of light above mentioned was noticed. On closing the eye, there was a marked diminution in the intensity of the light sensation ; this is due to the elimination of the beta rays, which are almost completely cut off by the eyelids, the residual effect being due to the gamma rays alone. The beta rays produce their effect by setting up fluorescence in the tissues in front of the retina, hardly any of them reaching the retina itself. With the gamma rays, on the other hand, the action is a dual one, being partly due to a fluorescence of the tissues of the eyeball, and partly to a direct action upon the cells of the retina itself. The direct effect of the gamma rays upon the retina was beautifully shown by the following experiment. "The radium was covered with 5 mms. of lead to cut off the beta rays, and a vertical plate of lead 40 mms. deep and 2 mms. thick was moved backwards and forwards over the radium, so as to form a bar-like screen 40 mms. thick and 2 mms. wide between it and the eye ; the effect produced was that of a bar of shadow moving across the glow. Now the gamma rays are not refrangible, and therefore the vertical lead screen would cast a partial shadow its own breadth upon the lens and retina. The effect upon the lens would be to diminish its fluorescence, but as the light waves are given off in all directions from the lens, there would not be a definite shadow upon the retina. Therefore this bar-like shadow must be due to the shadow on the retina itself."

Examination of the visual purple. In some respects the luminous effects produced by radium, applied in the manner described, present analogies with the response evoked by light of low intensity ; and as this latter is apparently connected with the visual purple, the effects of radium rays upon this substance were investigated. For this purpose the eyes of the frog or rabbit were used, the method of procedure being as follows. The animal, after being kept in darkness for several hours, was killed ; the retinæ were removed (in sodium light), one exposed to 50 mgs. of radium bromide for 20 hours in a moist chamber,

while the other, also kept in a moist chamber, served as a control. In no case was any difference noticeable between the control and experimental specimens; while both, when exposed to daylight, bleached in a few seconds.

Luminous effects of the rays upon the eye-tissues. Many tissues when exposed to radium (covered with black paper, as before), can emit light in greater or less degree. Thus, the skin glows when so exposed, and fat and muscle do so strongly. As regards the eye-tissues, the fresh lens of an ox, sheep or rabbit showed marked luminosity on exposure; the cornea and vitreous humour did so to a less extent, while the retina itself glowed strongly.

A statement apparently contradictory to this was made by Greef, who was unable to obtain any but the very smallest amount of fluorescence in the tissues of excised eyes by exposing them to radium. As, however, his specimen of radium was enclosed in a thick leather case, it is probable that most of the beta rays were unable to get through, and such minute fluorescence as he obtained was due to the gamma rays; a condition of things quite in accord with the observations of Hardy and Anderson.

Action upon the peripheral nerves. (1) *The sensory nerves.* One of the first communications upon the analgesic power of radium was made by Wickham in 1906. Since that time, to enumerate the authors who refer to this property would be almost to give a bibliography of the clinical uses of radium. An interesting observation, however, was made by Morson in 1914; he noted that as a result of handling for two months platinum tubes containing radium, which were used in the hospital wards, he experienced a temporary loss of tactile sensation in his fingers, but the sensibility to heat and cold were very marked.

(2) *The motor-nerves.* The action of radium upon the muscle-nerve preparation of the frog has been the subject of a series of researches by Lazarus-Barlow and Dunbar.

It was found that exposure to the alpha, beta and gamma rays from 7 milligrammes of radium bromide was attended by a better maintenance of neuro-muscular irritability than in the case of the non-irradiated preparation. This was manifested in two ways: firstly, the irradiated preparation responded to a smaller electrical stimulus than the control; and secondly, it was found to have a longer life. The beneficial or stimulative

effects are exerted upon the nerve, and to a certain extent upon the muscle, while the nerve endings are apparently unaffected. If the beta and gamma rays alone from the same sample of radium bromide are allowed to act for a period up to nine hours, no noticeable effect is produced; hence the stimulative effects from the mixed radiation must be due to the alpha rays.

The elimination of radium. In dealing with the question of the elimination of radium which has been administered to an individual, we are faced with the same difficulties that have been encountered in previous chapters, namely, that different observers have used different species of animals, and also that the preparations of radium and their methods of administration have varied in different cases. As regards the salts of radium, the results vary according as the preparation is soluble or insoluble, and again, whether the administration was by mouth or by hypodermic injection. Radium emanation again, whether given by inhalation or in solution, either by the mouth or by injection, differs in its method of excretion from both soluble and insoluble salts of radium itself. For these reasons, the experiments of different observers will of necessity have to be considered more or less in detail.

Salant and Meyer investigated the excretion of radium bromide, injected subcutaneously, into different parts of the alimentary tract. The animals employed were dogs and rabbits, in which biliary fistulæ had been established. In order to eliminate any complications from the swallowing of saliva, and to separate the contents of the different parts of the alimentary canal, ligatures were placed at the cardiac end of the stomach, at the pylorus, below the opening of Wirsung's duct, and at the junction of the large and small intestines; in addition, the upper and lower ends of the cæcum were ligatured off in the case of the rabbits.

Quantitative details are not given, but radium bromide of an activity of 1000 was injected subcutaneously, after which the different sections of the alimentary canal and their contents, together with the bile and urine, were examined for the presence of radium.

In both dogs and rabbits, elimination was found to take place by the kidney, liver and small intestine. In rabbits the elimination through the large intestine was less than through the small

intestine, while in the cæcum it was but slight in one case and absent in the other. Two rabbits were subjected to double nephrectomy, in order to determine whether the elimination through the small intestine and the liver was affected by the removal of the kidneys ; no change was, however, detected.

The general conclusions reached by these authors as the result of their experiments, are that the channels for the elimination of radium seem to vary in different species, and in different animals of the same species.

TABLE 55.

	Normal Dogs		Normal Rabbits.		Nephrectomised Rabbits.	
	1	2	1	2	1	2
Stomach	–	–	+	–	±	–
Stomach contents	..	–	–	–	±	–
Intestine	–					
Intestinal contents	+					
Bile	+	+	+	+	+	+
Fæces	+					
Blood	+	+	..	–	±	
Kidney	+					
Urine	+	+	+	+		
Small intestine	..	–	+	–	+	–
Contents of small intestine	..	+	+	+	+	+
Large intestine	..	–	–	–	+	–
Contents of large intestine	..	–	+	±	+	–
Cæcum	..	..	–	–	–	–
Contents of cæcum	..	..	–	±	–	–

Table, modified from Salant and Meyer, giving their findings regarding the presence of radium in different situations after subcutaneous injection of radium bromide.

+ = Active. ± = Slightly active. – = Inactive.

Dominici and Faure-Beaulieu injected .05 milligramme of radium sulphate into the marginal vein of the ear of a rabbit, the animal being killed eighteen months later. No morbid changes were detected, with the exception of some small patches of congestion at the bases of the lungs. The viscera were incinerated, and the relative degree of radio-activity of each

was determined by electrical methods; taking the activity of uranium as unity, and comparing equal areas of uranium and of the ashed organs, the following figures were obtained:

Organ		Organ	
Lung	.1	Liver	.7
Kidney	.1	Brain	.7
Spleen	.6		

Hence, eighteen months after intravenous injection of an insoluble radium salt, the internal organs were still definitely radio-active. In another rabbit, however, to which .02 milligramme of radium sulphate had been similarly administered, no trace of radium could be found thirteen months after injection.

An analogous experiment was that of Dominici, Petit and Jaboin, who injected one milligramme of radium sulphate, suspended in 250 c.c. of serum, into the jugular vein of a horse. Regular examinations of the urine showed the presence of radium, in gradually decreasing amounts, for a period of six months after the injection.

Lazarus-Barlow injected mice subcutaneously with radium silicate, and examined the animals, as they died, at various dates after injection. In his experiments no attempt was made to determine the distribution of radium in the various organs, but the whole animal was incinerated, and the total amount of radium present determined by means of an emanation electroscope. Taking the original amount of radium introduced as 100, the relative figures found in the animals dying in different weeks after inoculation were as follows:

Amount of radium introduced	= 100 units.
Found 1st week after inoculation	= 62 ,,
,, 2nd ,, ,,	= 27 ,,
,, 3rd ,, ,,	= 21 ,,
,, 4th–7th ,, ,,	= 14 ,,

A further series of observations regarding the distribution of radium in the various organs, after its administration either by the mouth or by injection, was made by Bellingham Smith. Mice were selected as the experimental animals, and measurements were made of the radium-content of various organs after the administration of a measured quantity. When the quantities to be dealt with were small, the observations were made with

an emanation electroscope. His experiments fall into three groups :

(*a*) Elimination of soluble salts of radium, admixed with barium salts.

(*b*) Elimination of insoluble salts of radium, also admixed with barium salts.

(*c*) Distribution and elimination of pure radium salts.

The findings may be briefly summarised as follows :—

(1) After the administration of radium, either by mouth or by injection, a widespread degree of activity is manifested throughout the body.

(2) Elimination of radium takes place principally by the small intestine, to a less degree by the kidneys ; while in mice at any rate, there is no evidence that either liver or skin play any part in its excretion.

(3) The lungs show a high degree of activity. This is possibly due to their extreme vascularity ; but its constant presence at all times after inoculation, and the fact that the emanation is entirely eliminated by the lungs, suggests that an accumulation of radium takes place.

(4) After administration of the emanation in solution, a general radio-activity of very brief duration is caused throughout the body. Emanation is excreted almost entirely by the lungs, and only to a very small extent by the kidney.

(5) The duration of activity induced in the body differs very much, according to the nature of the preparation employed.

Soluble salts are rapidly eliminated, however administered. Insoluble salts given by the mouth are excreted directly by the bowel, and there is no evidence of any temporary absorption and circulation. When given by injection, very slow elimination takes place by the bowel.

(6) The elimination of emanation is very rapid, and was complete, even after administration in considerable doses, in so short a period as four hours.

Suguira and Failla exposed mice to various intensities of beta and gamma rays, the source being tubes of radium emanation which were fixed at definite distances from the animals.

The effects upon the growth of the animals were studied in some detail, and it was found that an increase in body weight occurred in those mice which were exposed to doses ranging from

1.9-2.4 milli-curie hours, but that a decrease in body weight compared with non-irradiated controls occurred when the dose was increased to 6.8 milli-curie hours. It is interesting to compare this result with the increase in body weight of rats exposed to small doses of X-rays, observed by Russ, Chambers and Scott (p. 312). They also showed that an adverse effect was obtained with large doses.

Suguira and Failla also made observations upon the action of the above doses in the production of sterility. It was found that permanent sterility was produced in female mice with a dose of 2.4 milli-curie hours, a dose which had no such effect upon the males. Under the experimental arrangements the testes were at a greater distance from the source of radiation than the ovaries, and they were better protected by the thicker layer of tissue in the path of the rays. Bearing these features in mind, the authors nevertheless conclude that the testes in mice are more resistant than the ovaries.

Exposure of a small animal like the rat to a source of radium amounting to several grams may cause disturbances sufficiently profound to lead to the death of the animal in a few days. Exposures short of this, lead to very significant changes in various organs and to pronounced effects upon the blood. Generally speaking, the white cells are more affected than the red cells. Cramer, Drew and Mottram showed that the number of platelets in the circulation could be very much reduced by exposing rats to the gamma rays from radium. They made the important observation that the resistance of the animal to infection is greatly diminished by the dose of radiation which produced this action upon the platelets ; moreover, the infective conditions may clear up again as the number of platelets is restored to the normal level. They were further able to show that practically the same sequelae occurred as a result of withholding the fat soluble vitamin from the diet of the animal. Experiments of this kind seem especially valuable as they point out the very important part that radiation may play in starting processes which, comparatively unimportant in themselves, may lead to profound disturbances in the animal.

Mottram has shown in this connection that small doses of gamma radiation, if continued for a sufficient time, may act in a measure deterrent to the general health. The condition may be

exaggerated to the extent of endangering life, and there seems little reason to doubt from the evidence brought forward by Mottram that loss of life may ensue among people who habitually handle radium unless strict provision be made for their safety.

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RADIUM EMANATION.

General effects. In spite of its chemically inert character, radium emanation, when present in any considerable quantity, is by no means inactive towards the human subject. According to Mesernitzky, it produces vertigo, headache, faintness, weakness and pains in the joints ; among its objective results, according to the same observer, are emaciation, albuminuria and hæmorrhages.

These symptoms are probably due to the action of the alpha rays, for the circumstances are just such as permit of the highly-ionising action of these rays to have full play throughout the tissues. It is equally hypothetical to suggest, as some have done, that lecithin is a cell constituent particularly influenced by alpha radiation, as the contra suggestion that the enzymes connected with purin metabolism undergo an enhanced activation under the influence of these rays.

The circulatory system. When inhaled, the emanation is taken up by the blood, to which and to the whole body, it imparts a temporary degree of radio-activity. According to Plesch, it has no special affinity for hæmoglobin, and indeed is slightly

less soluble in blood than in water. Emanation present in the blood, either as the result of absorption from the alimentary tract or of injection, is rapidly eliminated. Gudzent states that when so introduced, it disappears from the blood in from two to four hours. According to the same authority, when it is absorbed by inhalation in a closed space, an accumulation takes place in the blood; his calculations show that after a quarter of an hour the amount present in 1000 c.c. of blood is equivalent to that in one litre of the inspired air; after two hours this amount is increased five or six times; and after three hours, six or seven times. Gudzent offers no explanation of this accumulation, but merely records it as the result of his observations.

As regards the oxygen content of the blood, Loewy and Plesch assert that it is unaltered by the presence of the emanation, and also that the respiratory exchange is similarly unaffected. Kikkoji, on the other hand, studying patients undergoing the "emanation" treatment, found that in three patients the oxygen inspired and the carbon dioxide expired were increased in two cases and unaltered in one.

Maass perfused the isolated frog's heart with Ringer's solution, in which emanation was dissolved. The heart beat diminished in force and frequency, and eventually came to a standstill in complete diastole. Perfusion of the heart with normal Ringer's solution restored the beat, and by again perfusing with the emanation solution, the above-mentioned phenomenon was repeated.

Elimination of radium emanation. According to Pieper, when radium emanation is introduced into the blood stream, two-thirds of it rapidly passes by the venous blood stream to the lungs, where most of it is eliminated. All observers agree that its removal from the blood stream is very rapid, and, according to Bellingham-Smith, even after considerable doses, its disappearance is complete in four hours; the loss takes place almost entirely by the lungs, only a very small quantity passing away by the kidney, roughly speaking, about one-millionth part of the quantity inoculated may be recovered in the urine, subsequent to an intra-venous inoculation. The rapid elimination of the emanation by the lungs is unavoidable, if the gas has made its way into the blood stream. If a subcutaneous inoculation of the emanation in liquid paraffin be made, the viscous nature

of the fluid and the extreme solubility of the emanation in it render the region active for much longer periods than if saline solution be used.

The gastric secretion. According to Olszewski, the inhalation of radium emanation in an " Emanatorium " has no influence whatever upon the secretion of gastric juice.

Purin metabolism. The question as to whether radium emanation has any effect upon purin metabolism is of interest, on account of the very considerable claims made in support of the " Emanatorium " treatment of gout. The whole question was raised in a communication by Gudzent in 1910. According to this observer, mono-sodium urate is converted by a disintegration product of the emanation, namely radium D, into more soluble bodies, which are eventually broken down into ammonia and carbon dioxide. Experiments were accordingly made by placing gouty patients under " Emanatorium " treatment. Under this treatment it was claimed that the uric acid content of the blood underwent a marked diminution. For instance, in two cases, where before treatment the uric acid content was 10 milligrammes per 100 c.c. of blood serum, after three weeks' treatment the figure had sunk to 6 milligrammes per 100 c.c.

At the same time Fofanoff, by injecting mono-sodium urate into rabbits, produced artificial tophi. The animals were then treated with emanation, either in the " Emanatorium," or by injection of its solution; the tophi and adjacent tissue were then excised and microscopically examined. As a result of the action of the emanation, this observer records a diminution in the amount of leucocyte infiltration in the tissue surrounding the tophi, and further comes to the conclusion that the emanation has a solvent action upon the monosodium urate itself.

If it be granted that the emanation has beneficial effects upon gouty conditions, it is by no means clear by what processes this is brought about. The emanation rapidly reaches all parts of the body by the blood stream; the vascular endothelium is known to be extremely sensitive to radiations, so that if such beneficial results accrue, and they are due to enzymes, it may be that enzymes, which are normally intracellular, are diffused into the blood stream, and are thereby enabled to exert their power of purin-disintegration over a more extended field than normally.

Such a condition of affairs is by no means identical with the activation of an enzyme or enzymes, and indeed, as stated in Part II. (p. 95), the whole question of the action of radiations upon enzyme action requires accurate quantitative study, and a similar remark applies to the "emanation" treatment of gout and other conditions.

The foregoing criticism is by no means intended as depreciating the clinical value of emanation, whether taken by inhalation, injection or in solution by the mouth. Clinical observations can alone decide that question; but it is hoped that enough has been said to demonstrate the desirability of further researches upon the pharmacodynamics of the emanation and its products.

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X RAYS UPON THE ADRENAL SECRETION.

Zimmern and Cottenot investigated the effects of irradiating the adrenal region in the human subject. The individuals selected suffered from abnormally high arterial pressure, and the treatment was pursued with the object of ascertaining whether by the action of the rays upon the adrenals, it was possible to effect a reduction in pressure. In some cases it was found that a single exposure sufficed to produce a well-marked diminution in pressure, but in most cases a series of exposures lasting over several months was necessary to reduce it to normal.

A second series of experiments was made upon rats by Eisler and Hirsch. The animals were killed by very large doses of X rays, doses of 150–200X (Kienböck) being given over periods

of from eight to ten days. As soon after death as possible the adrenals were extirpated, and an extract made in physiological saline solution. As controls, the same weights of adrenals from normal animals were taken and similarly extracted. These extracts were injected into the jugular veins of rabbits, while the blood pressure was registered in the carotid. In the case of extracts of irradiated glands, the blood pressure rapidly rose, but very soon returned to the normal; in the case of extracts from normal adrenals a similar rise in blood pressure was observed, but the elevation was maintained for a considerable time. The results obtained were well marked in the case of four irradiated animals: in five others the findings were not satisfactory, owing to the fact that the extracts were not made until some time after death.

X RAYS UPON NITROGENOUS METABOLISM.

The main observations upon this subject appear to be those of Williams, who noted the action of the rays upon uric acid excretion in a pathological condition, myelogenous leukæmia. The patient was placed upon a fixed diet containing 25 grams of nitrogen per diem; the total nitrogen in the fæces and urine was estimated, and also the uric acid present in the urine. The investigation resolved itself into an estimation of the average nitrogenous excretion of the patient upon his standard diet, before and after exposure to the rays. The average daily excretion of uric acid for five days preceding the application of the rays was .4738 gram; irradiation was then practised for ten minutes each day, arrangements being made that the exposures which were to be given on each successive day should be given under exactly the same conditions. The quantity of uric acid excreted during the period of irradiation was distinctly above the normal, as is seen from the following figures:

TABLE 56.

Day.	Quantity of Uric Acid.	Day.	Quantity of Uric Acid.
1	.5100	4	.9391
2	.6682	5	1.0220
3	.5610	6	.9513

The average excretion per diem during the period of irradiation being rather over .7752 gram per diem, as against .4738 gram before the treatment was commenced.

A further interesting feature is that on two days the total nitrogen output exceeded the intake. On the fourth day of exposure to the rays, owing to an attack of vomiting, the total nitrogen intake was only 13.28 grams, while the output in urine and fæces was 14.92 grams. On the fifth day, again, the nitrogen intake was 16.01 grams, the output being 17.87 grams. The figures on the different days of treatment are given in the accompanying Table.

TABLE 57.

Day.	Nitrogen Intake	Nitrogen in Urine.	Nitrogen in Fæces.	Total Nitrogen Output.
1	24.27	14.27	3.60	17.87
*2	20.24	16.60	2.34	18.94
3	21.13	19.18	1.60	20.78
4	13.28	13.25	1.67	14.92
5	16.01	16.98	0.89	17.87
6	18.20	15.69	1.32	17.01

* X ray treatment started on second day.

Blood counts were made daily during this time; and a marked rise in the number of leucocytes was noted on the fifth day. On referring to the case books of the Royal Infirmary, Liverpool, where the observations were carried out, the author found that of seven similar cases also treated by X rays, an initial leucocytosis occurred in five, all within eight days of the first exposure.

A further feature of interest was a rise of temperature at night, while exposures to the X rays were being given; a similar temperature rise was seen in two other patients in the same institution under similar circumstances. These findings are in accord with those of Senn and of Bryant and Crane.

When the blood films from Williams' case were examined, it was noticed that, whereas before X-ray treatment, the leucocyte granules stained well by methylene blue, with successive exposures this reaction became less and less marked. Since the methylene blue combines with granules, which themselves are acid in charac-

ter, this phenomenon is regarded by the author as indicating a progressive decrease in this property; it will be noted also that this diminution in the acid nature of the granules corresponded with an increased output of uric acid in the urine.

The more extensive therapeutic use of X rays of high penetrating power has brought somewhat prominently to notice the general physiological effects which these rays may produce in man when larger doses are dispensed.

There is little doubt from the evidence already obtainable in the literature that these physiological effects may be of a very disturbing character, and that in a few cases they have been profound enough to cause death.

Rolleston has reviewed the literature on the subject at some length, and has attempted to explain on general medical grounds the variation which may occur in the onset of the constitutional symptoms in question. These symptoms may come on within a few hours of the X ray exposure or be delayed for as long as twenty days; in general, the shorter the latent period the more severe the constitutional disturbance. The immediate symptoms are malaise, lassitude, nausea, vomiting, headache and giddiness, and these should be distinguished from the graver constitutional effects which do not supervene as a rule for several days after the exposure. The acute symptoms, which are more likely referable in origin mainly to cellular destruction produced by the radiation, consist of gastro-intestinal and cardio-vascular toxaemia, uncontrollable vomiting, offensive diarrhœa with passage of blood, abdominal pain and distension, fever and profound prostration.

Rolleston gives good reasons for believing that some of the immediate symptoms are due to the ozone and other gases formed in the neighbourhood of high-tension machinery, and considerable attention is now directed towards improving the general conditions under which radiation treatment is carried out.

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CHAPTER XX

THE SELECTIVE AND DIFFERENTIAL ACTION OF THE RAYS

In the early days of the therapeutic application of radium, the term "selective action" was employed as representing that the rays from radium produced a greater effect upon some cells than upon others. There is no doubt that the same intensity of rays does produce very dissimilar effects upon cells of different varieties, but in spite of this fact, controversy has at times arisen concerning the appropriateness of the term. To some it has appeared to focus too much attention upon the rays and too little upon the thing irradiated; the terms "sensitiveness," "vulnerability" and "susceptibility" were then invoked as correctives, only to be challenged by the term "selective resistance"; this was intended to indicate that the cells would be more or less influenced by the rays according to whether they were able to oppose a small or large resistance to their action. The introduction of the term resistance brings with it the consideration of the manner in which the rays may act; it is purely hypothetical that they are resisted in the way which the word can suggest, and it may be asked whether the term "selective absorption" is not as appropriate as the others in suggesting that the more the rays are absorbed the greater action they have. It would appear, however, that no single term is capable of giving expression to the actual facts of the case and at the same time represent the singularities of the processes involved, when radiation of any particular type is transmitted through living cells.

The preceding pages have provided numerous instances of this "selective" action of the rays, from the lowest forms of vegetable and animal life to complex animal tissues. Studies upon

protozoa have shown that a wide variation exists in the response of these organisms to the same exposure, whether it be to beta rays or X rays. There are good reasons for associating an increased sensitiveness on the part of some of these organisms with an absence of chlorophyll in their composition. It is also worthy of note that the multi-nucleated forms suffer more than the mono-nucleated when exposed to these rays, and that in general the larger forms are more sensitive than the small ones. The crustacea exhibit differences among themselves of about the same magnitude as the commoner pathogenic organisms. Proceeding higher in the scale of development, experimental investigation has shown a wide range of vulnerability to exist among the various parts of the organism; the testicle has served in this respect not only to show a general sensitiveness of a marked order, but to exhibit within its structure some of the most striking evidence for the essentially selective action which the X rays possess; the seminiferous epithelium is quite destroyed by a quantity of radiation to which the cells of Sertoli appear practically indifferent. Mention may be made here of the high order of sensitiveness towards X rays exhibited by lymphoid tissue, by cartilage and by vascular endothelium. One of the earliest important generalisations upon this subject was made by Bergonié and Tribondeau, as a result of their classical experiments upon the effects of X rays on the testicle of the rat; they suggested that very rapidly-growing cells are the most affected of any by such radiations. Within limits there is truth in the assertion, but the whole truth is not conveyed by the statement, nor is it proven that rapidity of cell growth can be looked upon as a trustworthy guide in evaluating the probable response of any particular tissue when irradiated. This response, on the part of any particular type of cell, is in fact dependent upon the kind of rays to which it is subjected; in other words, different rays give rise to quite different effects upon one and the same variety of cell; they have in fact a "differential" action, and a careful distinction should be made between the differential action which different rays have upon the same variety of cell, and the selective action which the same kind of radiation has upon the many different varieties of cells.

The X-ray spectrum ever widens before the investigator, and at present a range of many octaves of wave-length confronts

one. If attention were restricted to any particular wave-length, there would be ample scope for a generalisation concerning the effects that such radiation has upon the many varieties of cells which constitute the tissues of the animal body. When this has been done for a large number of wave-lengths, broad generalisations may be attempted with more success than is possible at present.

One of the best examples of the differential action of X rays is afforded by clinical evidence; it has been shown that, whereas the human skin cannot be given more than what is known as a pastille dose of soft unscreened X rays without a dangerous degree of reaction occurring, it is quite otherwise when harder rays, *i.e.* rays of shorter wave-length are alone utilised; not only can very much larger doses be administered through the skin, but the reaction they produce is of a totally different kind to that provoked by soft rays, *i.e.* of longer wave-length. The importance of determining the differential action of the rays which are used clinically, upon the various types of malignant growth need not be dwelt upon here.

Within the last few years a considerable amount of research upon the differential action has been carried out, and it has been maintained by some that, provided equal amounts of energy are absorbed by the tissues of short and of long wave-length energy, then the reactions are the same. The question is a difficult one experimentally, and the answer cannot be given with certainty until a method for measuring the intensity of a beam of X rays is established which will be free of objections. It is customary for physicists to rely almost exclusively upon ionisation methods for this purpose, but, unfortunately, there is no uniformity in the ionisation chamber used for the purpose. Owing to the fact that when X rays strike solid surfaces they liberate secondary radiation, which is not only of a complex character but varies according to the nature of the solid and according to the wave-length of the radiation, it will be seen how essential it is to select some experimental arrangement which will avoid these complications as far as possible. It seems hardly profitable at the present stage to cite experiments by one observer with one type of measuring instruments which would be strongly controverted by another observer having a different experimental arrangement. It is hoped that steps will soon be taken to adopt some unit of X ray intensity which will have international sanction.

A considerable amount of evidence has accumulated to show that not only does one variety of cell react in a different degree to another when exposed to the same type and intensity of radiation, but that a single cell will exhibit a widely varying degree of reaction according to the particular phase of its life-cycle, in which it happens to be at the time that it is irradiated. We may instance the fact that certain ova have been found to be nearly eight times as vulnerable to beta rays when they are in an active state of division as when they are in a resting stage. Facts of this kind indicate one of the difficulties of quantitative investigations upon living tissues; for in almost any large collection of cells, every phase of the life-cycle will be represented, each with its own degree of susceptibility. It also suggests, without however proving, that the differences which have been shown to exist between the effect of an intense radiation acting for a short time, and that of a weak radiation acting for a correspondingly longer time, may be to some extent associated with the varying susceptibility of the cell during its development to maturity.

Physical research has shown that the absorption of different types of rays by metallic screens is a highly complicated process, and in all probability absorption by living tissues is a phenomenon of no less complexity. The chemical composition of the cell, varying as it does from point to point, may determine to a considerable extent the degree of change brought about by irradiation. In sections of one and the same malignant growth, taken before and after irradiation, the staining reactions point to as marked changes in chemical composition as the morphological features indicate modifications in the cell type.

The obtaining of such specimens after the tissue has been submitted to various periods of irradiation under specified conditions, their examination and observation of the order in which changes occur in cells of given types are gradually providing data which can hardly fail to be of fundamental importance in the construction of a rational basis of radio-therapy. It would appear quite certain that rate of growth alone cannot determine the subsequent behaviour of cells when they are irradiated, for malignant growths, differing inappreciably in their rate of development, are often observed to react in an entirely different manner and degree under identical conditions of exposure.

CHAPTER XXI

BRIEF SUMMARY OF FACTS AND THEORIES

In the preceding pages we have given an account of the phenomena observed when living tissues are exposed to radiation. It now remains for us to review broadly the experimental results, and to see if it is possible to arrive at any general conclusions regarding the action of the rays. The question is admittedly a very complicated one, yet it may be possible to summarise certain facts in such a way as to prepare the ground for further clinical and experimental work.

In discussing any "Laws" which may be put forward it is essential to recognise the fact that all such "Laws" are merely more or less succinct statements of our present knowledge upon the subject, and that they are of necessity liable to alteration in the light of future discoveries. In the present connection, such a warning seems especially necessary since the subject under discussion is a very youthful one. Only recently has the nature of the X rays and of the γ radiations from radium been placed beyond controversy, and the continuity of the X-ray members of the electromagnetic spectrum with the ultra-violet region been conclusively demonstrated.

A simple example of the complicated nature of the problems under investigation is afforded by the action of the X rays upon bacteria. Clinical experience furnishes abundant evidence of the beneficial effect of radiations in the treatment of pyogenic cutaneous lesions and of tuberculous lymphatic glands. Yet the dose of X rays necessary to produce a lethal or even an inhibitory effect upon bacterial growth is many times greater than could be tolerated by the human tissues. Here there is manifestly another factor to be considered besides the radiations and the bacteria concerned, and that is the reaction of the animal tissues. Nor

does the matter end here, since from various experiments it is known that soft and hard X rays in equal doses do not cause similar reactions. In this one instance then, we see that at least three variables have to be considered—the resistance of the bacteria, the reaction of the tissues, and the wave-lengths of the radiations employed.

Attempts at generalisations concerning the action of radiations upon living tissues fall into two well-defined and distinct groups. In the first category come what may be termed Laws of Effects of the radiations. Such laws are merely statements of experimental or clinical observation, and must stand or fall according to whether subsequent investigations confirm them or otherwise.

In the second category come theories regarding the mode of action of the rays, and here the attempt is more ambitious, since it involves speculation into the nature of the processes which occur throughout these living structures when they are subjected to irradiation.

We shall first endeavour to summarise some of the outstanding experimental findings and then proceed to discuss theories of action.

Laws of the effects of radiations. It will be convenient in the first place to enumerate such of the effects of radiations as can fairly be expressed in the present state of our knowledge, since the groundwork of experimental fact must be extensive and indisputable before time can profitably be spent in speculations upon the nature of the processes involved.

(1) *The cells of some tissues are more affected by a given dose of radiation than are the cells of other tissues when exposed to the same dose.*

This is generally termed Selective Action, and numerous examples have been recorded in the previous pages of this book. Not only is this the case with the cells of different organs considered as a whole, but even with particular groups of cells in the same organ. A good example of this is seen in the testis. Another example is to be found in the report of the action of heavy doses of the γ rays of radium upon the kidney (*Med. Res. Council Spec. Report,* Series No. 62). Here it was possible to observe in one and the same microscopic field that the cells of the convoluted tubules had undergone marked vacuolation and degeneration, while the cells of the conducting tubules were apparently but little affected. It is obvious that the amount of radiation to

which both types of cell were exposed must have been practically identical in the two cases.

Similarly, in observing the effects of radiations upon developing forms, certain groups of tissues are found to be more affected than others, although all the tissues have been exposed to the same radiations.

(2) *In some cases, at least, the cells of a tissue are more affected by a given amount of energy of one range of wave-lengths than they are by the same amount of energy of another range of wave-lengths.* This we have spoken of as Differential Action. The classical example is seen in the effect of radiations upon the human skin, which cannot be subjected to more than a single " pastille dose " of soft unscreened X rays without severe reaction ensuing. The dose can, however, be markedly increased without the production of untoward results if harder rays—*i.e.* rays of shorter wave-length—are used.

(3) *Some cells when in an active state of division are more affected by a measured dose of radiation than are similar cells in the resting stage.* This has not been demonstrated in many types of cells, but among those investigated in this connection the cells of the testes and the ova of *Ascaris* are perhaps the best known. In the case of these ova, not only has it been shown that this special sensitiveness occurs in cells whose nuclei exhibit active division, but that one special phase of division—the metaphase—manifests it in an enhanced degree.

(4) *Some cells respond to a dose of radiation in different ways, according to whether such radiation is administered so that a large intensity is coupled with a short period of exposure, or a small intensity is coupled with a long period of exposure.*

This has been shown to be true of the action of radium emanation upon the brains of young animals. And it has also been shown that β rays acting upon the human skin produce a more destructive effect when a source of high intensity acts for a short time than when a source of low intensity acts for a correspondingly long time.

(5) *Some cells are stimulated in their growth by a small dose (or doses) of radiations; but inhibition of growth or damage results from the administration of large doses.*

Definite evidence of cell stimulation by X rays or radium is difficult to obtain. In the case of animal tissues which exhibit hypertrophy as the result of irradiation, we are by no means

dealing with a simple case, and it is perhaps unfortunate that the same word stimulation is used to denote the hypertrophy which may arise as a result of a complex series of processes in the animal organism and the hastening of the mitotic activity of unicellular organisms when exposed to very small doses of radiation. There is frequent reference in clinical literature to the increased rate of growth of malignant tumours after inadequate irradiation, but how far this is a direct result of the radiation upon the malignant cells and how far it is due to the reaction of the normal contiguous tissues is not easily determinable.

(6) *Differences exist in the Latent Periods when tissues are exposed to the radiations.*

In general it may be said that a considerable interval of time is necessary before any changes, that can be detected macroscopically or microscopically, occur in irradiated tissues. The interval ranges from a few hours (*vide spleen*) to several weeks (*vide skin*), and in this respect it is worth noticing that the exposure of the skin to ultraviolet radiation may be followed by a marked reaction within the course of a few minutes.

Theories of action. When we come to theories concerning the mode of action of the radiations upon living tissues, it would seem that sufficient experimental evidence has not been forthcoming to tempt many in this direction. In the early years there was a tendency to direct attention to some definite part of the cell—for instance, the nucleus—as essentially the region where destructive effects originate. On other occasions some particular cell-constituent—for example, lecithin—was indicated as being decomposed by the radiations, and the changes in the cell were attributed, either wholly or in part, to the action of its decomposition products.

The time for the statement of a general theory to explain the mode of action of the radiations has doubtless not yet arrived; but it may not be unprofitable to consider certain aspects of the question which seem fundamental.

One aspect is that of equilibrium. It is a commonplace that any living structure is a complex involving a number of interdependent equilibria; if one of these be upset, the others are immediately involved. In normal conditions these equilibria are in a continual state of adjustment. The interchange of gases in the respiratory system, of solids and fluids in the excretory system,

are examples of equilibrium, where the system involved is capable of continual readjustment, provided that it has not been subjected to too great changes, either by disease or by experimental intervention.

In radiation, it is clear that we have an agent which is capable of disturbing the normal equilibria in the parts irradiated. Small doses of radiation, generally speaking, give rise to transient effects, while more intense radiation produces permanent damage or complete destruction. In the former case, the disturbance of equilibrium has been so slight that a more or less complete restoration is possible, in the latter the alteration has been so profound as to prevent a return to normal conditions. What special equilibria are most sensitive to the action of radiation it is for experiment to determine; and it must be borne in mind that we are concerned not only with the equilibria in the cell itself, but with those existing between the cell and its surroundings.

Pathologists generally are agreed that malignant growths are disorderly in the sense that they do not conform to the controlling processes which normally govern the tissues of the body. Here there are obviously three groups of equilibria which may have to be considered, namely:

(1) Those occuring in the normal tissues.
(2) Those occurring in the neoplasm itself.
(3) Those occurring between the neoplasm and the normal tissues.

It is an undisputed fact that, in some cases at least, radiations have a very marked inhibitory effect upon the growth of neoplastic tissues. The question then arises as to whether the regressive change is produced by the action of radiation upon the neoplastic cells or upon the surrounding normal tissues. Since the most marked histological changes occur in the neoplasm itself, it would seem that it is here the main seat of action is to be sought. Nevertheless, it is clear that the radiations cannot be without effect upon the surrounding tissues, and indeed the extensive development of fibrous tissue which often replaces a mass of neoplastic cells as a result of irradiation seems to afford evidence of this. Other studies upon the normal tissues leave no room for doubt as to the important part which their reactions play in the ultimate result of the treatment of disease by radiation.

A few words may be said about the nature of cell contents.

Simple electrolytes are not likely to be altered in any of their purely electrical relations by the rays under discussion ; for the number of ions produced per cubic centimetre in solutions of electrolytes by exposure to intense radiation is insignificant in comparison with their normal contents. This is, however, not the case with some of the more complex cell constituents. We have already referred to the changes occurring in colloids as the result of radiation, and though a great deal more work must be done before the action of radiations on colloids is even partially understood, it would seem that here we have at least a starting-point for investigations which should help in elucidating the problems we are now considering.

The time elapsing between irradiation and the appearance of any obvious changes in the colloid present at least a suggestive parallel with the latent period which elapses between, *e.g.* irradiation of the skin and the appearance of a visible reaction.

There is another aspect of equilibrium which cannot be omitted, and that is the normal balance between the intracellular enzymes and the other cell constituents. It is undoubtedly true, in some cases at least, that irradiated tissues undergo autolysis to a greater extent than non-irradiated tissues of the same kind. From this it has been concluded that the intracellular enzymes undergo actevation as a result of irradiation. As we have already indicated, statements regarding the action of radiations upon enzymes are very contradictory, and we have offered some suggestions as to the reasons for these widely divergent statements. It is clear that in considering any enzymic action we have to take into consideration not only the enzyme, but the substance upon which it acts. Interference with the colloidal equilibrium of the cell would tend to destroy its vitality wholly or in part, and the normal resistance of the cell to the disintegrating powers of its own intracellular enzymes might thus be diminished.

We have referred to the importance we are inclined to attribute to conditions of equilibrium in living processes. In most cases, of course, more than one equilibrium has to be considered, but in some cases it may be possible to indicate the forces which may be looked upon as those dominating the equilibrium. For instance, the behaviour of a leucocyte in the blood stream is more likely to be controlled by the forces of surface tension than by the internal forces governing its metabolism.

Concerning forces of a purely electrical character, it is known that the body is the seat of electrical currents which are of sufficient magnitude to serve as a basis of diagnosis in cardiac affections; it is also known that the double layer of electricity at the cell interface, known as the Helmholtz double layer, is an electrical feature of all organisations, and, moreover, one of extraordinary stability. It may indeed be questioned whether this double layer would be altered to any appreciable extent by intense beams of X rays.

In discussing Theories of Action we may ask ourselves the question whether it is not bordering upon presumption at the present stage to suggest any General Theory of the effects of radiation upon living structures. We have strong ground for thinking that one single theory of action could not possibly carry the burden of experimental fact with which it would be immediately loaded. To illustrate this point, let us take as an example the irradiation of a malignant mass at a depth in the body by X rays applied externally. Let us assume that the main symptoms following this are (1) an inflammation of the skin, (2) a diminution in the size of the tumour, and (3) cessation of pain. Is it rational to ask for one single theory of action which will include such widely different effects? If not, the alternative seems that the subject is one which, embracing as it does so many essentially different processes, must be studied in detail, then, when each authenticated effect has a reasonable working theory of the processes operating, a comprehensive grouping and coordination may be attempted.

The way towards any working theory of action must in the first instance be gained by accurate observation; with such a basis theory will predict how further facts may be ascertained. It must be realised that we are only at the threshold of the subject; ever-increasing co-operation between the chemist, the clinician, the pathologist, the physicist and the physiologist will help to solve the problems involved in considering the mode of action of the rays. In radiology applied to biological problems there is a double difficulty, for the intensity of the radiation used, whether it be X rays or radium, is a quantity which under many experimental conditions presents very considerable difficulties in its accuracy of measurement, and the animal itself provides a complex which refuses to be reduced to simple terms.

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X RAYS AND CRYSTAL STRUCTURE

BY

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